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The benefits (or detriments) of adapting to demand disruptions in a hospital pharmacy with supply chain disruptions

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Abstract
Supply chain disruptions and demand disruptions make it challenging for hospital pharmacy managers to determine how much inventory to have on-hand. Having insufficient inventory leads to drug shortages, while having excess inventory leads to drug waste. To mitigate drug shortages and waste, hospital pharmacy managers can implement inventory policies that account for supply chain disruptions and adapt these inventory policies over time to respond to demand disruptions. Demand disruptions were prevalent during the Covid-19 pandemic. However, it remains unclear how a drug's shortage-waste weighting (i.e., concern for shortages versus concern for waste) as well as the duration of and time between supply chain disruptions influence the benefits (or detriments) of adapting to demand disruptions. We develop an adaptive inventory system (i.e., inventory policies change over time) and conduct an extensive numerical analysis using real-world demand data from the University of Michigan's Central Pharmacy to address this research question. For a fixed mean duration of and mean time between supply chain disruptions, we find a drug's shortage-waste weighting dictates the magnitude of the benefits (or detriments) of adaptive inventory policies. We create a ranking procedure that provides a way of discerning which drugs are of most concern and illustrates which policies to update given that a limited number of inventory policies can be updated. When applying our framework to over 300 drugs, we find a decision-maker needs to update a very small proportion of drugs (e.g.,$<5\%$) at any point in time to get the greatest benefits of adaptive inventory policies.

Keywords Inventory management · Supply chain management · Simulation · Pharmaceutical drugs · Healthcare · Operations research · Operations management

Highlights

- Adaptive inventory system that captures perishability, supply chain disruptions, and demand disruptions
- Ranking procedure to discern which medications are of most concern and illustrates which medications to adapt given that a limited number of inventory policies can be updated
- For a fixed mean duration of and mean time between supply chain disruptions, a medication's shortage-waste weighting dictates the magnitude of the benefits (or detriments) of adaptive inventory policies
- For a fixed shortage-waste weighting and long-run probability that the supply chain is disrupted, if adaptive inventory policies are beneficial, the benefits generally decrease as the supply chain disruption duration increases
- Decision-maker needs to update a very small proportion of medications (e.g., $< 5\%$) to get the greatest benefits of adaptive inventory policies

1 Introduction

Hospital pharmacy managers are responsible for determining how much inventory to have on-hand and when to place orders. Key aspects that need consideration when making these inventory decisions are supply chain disruptions and demand disruptions. A supply chain disruption is a random amount of time such that the hospital pharmacy is unable to receive a particular medication [1]. There are many possible causes of supply chain disruptions in a hospital pharmacy inventory system (e.g., manufacturing issues, quality issues, raw materials, natural disasters [2–4]). The resiliency of pharmaceutical supply chains is an active area of concern [5].

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Insufficient inventory during these supply chain disruptions leads to drug shortages which can increase costs, increase medication errors, and decrease the quality of care [2, 6, 7]. Shortages in a food inventory system may cause you to change your recipe and shortages in a concert inventory system may cause you to miss your favorite band. However, drug shortages in a hospital pharmacy inventory system can cause significant drawbacks such as patients experiencing denied/delayed care (e.g., cancelled surgeries) or being provided with sub-optimal treatment (e.g., substitute medications with less efficacy or more side effects). A simple solution is stocking more inventory than is needed, but holding too much inventory leads to waste as medications have a finite shelf life. For clarity, throughout this research, we use the term "medication" to refer to a particular pharmaceutical medication/SKU (e.g., Labetalol). We use the term "drug" to describe the drug doses for a particular medication of interest (e.g., drug shortages [for a particular medication], drug waste [for a particular medication], holding cost per day per drug, proportion of drug shortages, proportion of drugs wasted).

Balancing the drug shortage versus drug waste trade-off is further complicated by demand disruptions. Demand disruptions occur when the demand mean is different from "normal/baseline" (i.e., it increases or decreases) for a random or extended amount of time. Demand disruptions were prevalent during the Covid-19 pandemic (e.g., surges in demand to treat Covid-19 patients and declines in demand for other medications due to the cancellation of elective surgeries). Failing to adapt to disruptions that increase or decrease demand often leads to drug shortages and drug waste, respectively. However, medications differ in their shortage-waste weighting (i.e., concern for shortages versus concern for waste) and supply chain disruption profile (i.e., duration of supply chain disruptions and time between supply chain disruptions). The duration of a supply chain disruption refers to the time between when the supply chain disruption begins and the time that the supply chain disruption ends. The time between supply chain disruptions refers to the time between when one supply chain disruption ends and the time that a new supply chain disruption begins. We are interested in studying how these differences influence the benefits (or detriments) of adapting to demand disruptions.

A medication's shortage-waste weighting defines the shortage concern versus waste concern for a particular medication of interest. Defining a medication's shortage-waste weighting helps to capture the trade-off between drug shortages and drug waste. With the varying medication shortage-waste weightings and supply chain disruption profiles, simulation modeling is a viable method to assess the performance of the inventory system given different inventory policies, such as adaptive inventory policies (i.e., inventory policies change over time), are in place.

To analyze the performance of adaptive inventory policies, we recognize that hospital pharmacy managers decide how frequently to place orders and how much inventory to have on-hand. To this end, we develop an adaptive lost-sales (R, S) periodic review inventory system where R denotes the length of the review period (i.e., attempt to place an order every R days) and S denotes the order-up-to level (i.e., attempt to place an order up to S every R days). By lost-sales, we imply that if a patient needs a medication that has zero inventory on-hand, the demand for that specific medication is lost and consequently, a shortage cost is incurred. In a hospital pharmacy setting, this patient who needs a medication that has zero inventory on-hand may receive a substitute medication or have delayed/cancelled treatment. By adaptive, we imply that the (R, S) inventory policy changes over time to reflect the shifts in the demand mean. We design the adaptive inventory system such that it (1) solves for the (R, S) inventory policy in a hospital pharmacy with supply chain disruptions, (2) endogenously detects when the inventory policy needs to be updated due to a demand disruption, and (3) appropriately updates the (R, S) inventory policy. Contracts, logistics, and resources can make it challenging to update the (R, S) inventory policy very frequently. We use the medication's shortage-waste weighting, the change in the expected proportion of drug shortages per day, and the change in the expected proportion of drugs wasted per day to support when the (R, S) inventory policy needs to be updated. Furthermore, we recognize that hospital pharmacy managers are often responsible for thousands of different medications. To provide quick solution times and easy implementation, we create an adaptive inventory system that consists solely of closed-form expressions. Closed-form expressions provide quick solution times and easy implementation because the output (e.g., optimal inventory policy, proportion of drug shortages per day, proportion of drugs wasted per day) can be expressed/calculated as a function of input parameters. Although, hospital pharmacy managers may only be able to adapt a limited number of (R, S) inventory policies at any given time. To give these managers a sense of which medications are of most concern, we use the adaptive inventory system and provide a procedure to rank medications based on multiple characteristics of a medication (e.g., expiration lifetime, shortage concern, waste concern, demand for the medication).

This research makes the following contributions:

1. We create an adaptive (R, S) periodic review inventory system that accounts for perishability, supply chain disruptions, and demand disruptions. All expressions are presented in closed-form providing quick solution times and easy implementation which is critical in a hospital pharmacy where managers are often responsible for thousands of different medications.

2. The adaptive inventory system relies on the expected proportion of drugs wasted per day in a (R, S) periodic review perishable inventory system with supply chain disruptions and stochastic demand. To the best of our knowledge, we are the first to present this value in closed-form.
3. We use the adaptive inventory system to create a ranking procedure. The ranking procedure provides a way of discerning which medications are of most concern and illustrates which policies to update given that a limited number of inventory policies can be updated.
4. We leverage simulation modeling and perform an extensive numerical analysis using real-world demand data from the University of Michigan's Central Pharmacy to distinguish how a medication's shortage-waste weighting and supply chain disruption profile influence the benefits (or detriments) of adapting to demand disruptions.

The remainder of the paper is organized as follows: Section 2 provides literature relevant to this research. Section 3 presents the adaptive inventory system and the ranking procedure. Section 4 presents the simulation models of the multiple inventory systems we consider in this research. In Section 5, we conduct a numerical analysis using real-world demand data from the University of Michigan's Central Pharmacy. Section 6 closes the paper and provides future research directions.

2 Literature review

Disruptions in a supply chain, whether from demand, supply, or transportation, are not a new problem. Paul et al. [8], Snyder et al. [1], Shen and Li [9], and Ivanov et al. [10] provide insightful review articles on the topic. To demonstrate how this research expands upon past research, we organize the relevant literature into two areas: inventory models without disruptions and inventory models with disruptions. We close this section by using past literature to motivate adaptive inventory policies in a hospital pharmacy setting.

In Table 1, we present (a) inventory models without disruptions, (b) inventory models with disruptions, and (c) this research. For each paper, we characterize the research by perishability (NP: non-perishable, P: perishable), demand (D: deterministic, S: stochastic, DD: demand disruptions), supply (SSC: stochastic supply capacity, SLT: stochastic lead time, SCD: supply chain disruptions), adaptive (i.e., inventory policy/control parameters change over time or research uses thresholds to incorporate dynamic decision-making), and methodology. We note that if the authors consider a perishable inventory system (e.g., hospital pharmacy), but the authors do not capture perishability in their model (i.e., the authors do not capture the finite lifetime of the product), we label the paper as NP (i.e., non-perishable).

In comparison to the literature, we would like to motivate adaptive inventory policies and the importance of assessing the performance of the inventory policies for a hospital pharmacy inventory system. From a hospital pharmacy perspective, Ivanov et al. [27] creates a simulation model to study a multi-echelon pharmaceutical supply chain faced with supply chain disruptions. The findings from [27] suggest that adaptive inventory policies (i.e., inventory policies change over time) may help decrease drug shortages and costs for an inventory system with supply chain disruptions. The author suggests adaptive inventory policies for future research. It is worth noting that demand disruptions are not taken into consideration in this earlier research. It is also worth noting that we incorporate supply chain disruptions when solving for the optimal inventory policy and we adapt the inventory policy over time to account for demand disruptions to overcome drug shortages and drug waste.

From a disruption perspective, Snyder et al. [1] discuss the need for integrating proactive (i.e., guard against future uncertainties) and reactive (i.e., implemented when unexpected events occur) strategies when overcoming disruptions [10]. In this paper, we account for supply chain disruptions when solving for the optimal (R^*, S^*) inventory policy [proactive] as well as endogenously detect demand disruptions and update the (R^*, S^*) inventory policy [reactive] to tackle the drug shortage and drug waste challenges in a hospital pharmacy inventory system. Furthermore, by detecting demand disruptions and appropriately updating the (R^*, S^*) inventory policy, we are able to adapt to changing conditions and consequently, improve the viability of the inventory system [36].

Also, we leverage simulation modeling because it is a viable method to assess the performance of an inventory system given different inventory policies, such as adaptive inventory policies (i.e., inventory policies change over time), are in place. It is also worth noting that we are analyzing the performance of an inventory system with many complexities (e.g., perishable (R, S) inventory policy, supply chain disruptions, real-world demand data, adaptive inventory policies) and simulation modeling has the flexibility to capture all of these complexities. When considering the performance of an inventory system, we consider varying medication shortage-waste weightings (i.e., concern for shortages versus concern for waste) and supply chain disruption profiles (i.e., duration of and time between supply chain disruptions). Gebicki et al. [37] encourages the use of the criticality of the medication (i.e., concern for shortages defined by a medication's shortage-waste weighting in this research) and availability

Table 1 Summary of relevant literature

Paper	NP/P	Demand	Supply	Adaptive	Methodology
(a) Inventory models without disruptions					
Zhang et al. [11]	NP	D			Simulation-optimization
Little and Coughlan [12]	NP	S			Constraint program
Neve and Schmidt [13]	NP	S			Cost/service level optimization
Peterson et al. [14]	NP	S		✓	Heuristics for dynamic program
Kim et al. [15]	NP	S		✓	Reinforcement learning
Eilon and Elmaleh [16]	NP	S	SLT	✓	Forecasting procedure
Dillon et al [17]	P	S			Stochastic program
Kara and Dogan [18]	P	S			Reinforcement learning
Rajendran and Srinivas [19]	P	S			Stochastic program
Syawal and Alfares [20]	P	S			Simulation-optimization
Xu and Szmerekovsky [21]	P	S			Stochastic program
Li et al. [22]	P	S		✓	Dynamic program
Li et al. [23]	P	D	SLT		Nonlinear program and closed-form
Franco and Alfonso-Lizarazo [24]	P	S	SLT		Stochastic program
Nguyen and Chen [25]	P	S	SSC		Stochastic program
Nguyen and Chen [26]	P	S	SSC		Stochastic program
(b) Inventory models with disruptions					
Azghandi [27]	NP	S	SCD		Simulation model
Schmitt et al. [28]	NP	S	SCD	✓	Simulation model
Atan and Rousseau [29]	P	D	SCD		Closed-form
Czerniak et al. [30]	P	D	SCD		Closed-form
Saedi et al. [31]	P	S	SCD		Continuous time Markov chain
Czerniak et al. [32]	P	S	SCD		Simulation-optimization
He and Wang [33]	P	DD			Analytical model
Rana et al. [34]	P	DD			Analytical model
Uthayakumar and Karuppasamy [35]	P	DD			Economic order quantity model
(c) This research					
Czerniak et al. (2024)	P	DD	SCD	✓	Closed-form framework

NP: non-perishable, P: perishable, other abbreviations defined in Section 2

of the medication (i.e., supply chain disruption profile in this research) in inventory decision-making to improve the outcomes of a hospital pharmacy. But, they do not study adaptive inventory policies.

3 Adaptive (*R*, *S*) inventory system

We proceed to present the adaptive (R, S) inventory system. We start by presenting how to solve for a (R, S) inventory policy for a perishable inventory system with supply chain disruptions (in Section 3.1) and how to adapt this (R, S) inventory policy over time to respond to demand disruptions (in Section 3.2). We close this section by presenting a ranking procedure (in Section 3.3) which provides a way of discerning which medications are of most concern and illustrates which inventory policies to update given that a limited number of inventory policies can be updated.

3.1 (*R*, *S*) inventory policies with supply chain disruptions

We start by modeling a lost-sales (R, S) perishable inventory system with supply chain disruptions as done in Czerniak et al. [30]. Here, R represents the length of the review period (i.e., attempt to place an order every R days) and S represents the order-up-to level (i.e., attempt to place an order to raise the inventory position up to the order-up-to level S every R days). The closed-form expressions derived in Czerniak et al. [30] provide quick-to-solve and easy-to-implement (R, S) periodic review inventory policies. We simply refer to this model as the (R, S) model. In Table 2, we present the notation for the (R, S) model. Then, we proceed to present a summary

Table 2 Summary of the modeling notation for the (R, S) model [30]

Notation	Description
Input parameters	
k	Fixed ordering cost (i.e., for each order attempted; $k > 0$)
h	Holding cost per day per drug ($h > 0$)
q	Deterministic demand per day ($q > 0$)
e	Expiration lifetime in days ($e \geq 1$)
γ	Maximum proportion of drug shortages per day over the infinite horizon ($0 < \gamma < 1$)
$\alpha^{(R)}$	Supply chain disruption probability with respect to the length of the review period R ($0 < \alpha^{(R)} < 1$)
$\beta^{(R)}$	Supply chain recovery probability with respect to the length of the review period R ($0 < \beta^{(R)} < 1$)
Variables	
R	Length of the review period ($R \geq 1$)
S	Order-up-to level ($S \geq 0$)
m	Number of review periods S fully covers ($m = \lfloor \frac{S}{qR} \rfloor$; $m \geq 1$)

of the model assumptions. We also describe the structure of the model and provide support for the assumptions made.

Summary of Modeling Assumptions for the (R, S) Model

- Deterministic expiration lifetime e
- Deterministic and static daily demand q
- Zero lead time
- Orders can only be attempted at times that are integer multiples of R
- Orders are only successfully placed when the supply chain is not disrupted
- Always have full and accurate knowledge of the inventory on-hand
- Supply chain disruptions modeled as a two-state discrete time Markov chain
- Medications have no quality decay
- Expiration lifetime e starts when the medication arrives at the pharmacy
- First-in-first-out protocols in place

Model Structure and Support for the Assumptions Made for the (R, S) Model

The (R, S) model minimizes the expected ordering and holding cost, while constraining the proportion of drug shortages per day to be at most γ over an infinite horizon. Through discussions with our hospital pharmacy collaborators, an ordering cost is necessary to capture the work associated with placing/receiving an order. Furthermore, if an ordering cost is not included, the model would set the length of the review period R to $R = 1$ for every medication in the hospital pharmacy inventory system (i.e., an order would be attempted for every medication every day). In Section 5.3, we describe how we estimate the ordering cost and holding cost input parameters. The constraint on the proportion of drug shortages per day is tight with the optimal (R^*, S^*) inventory policy (i.e., the proportion of drug shortages per day is γ over an infinite horizon). The model also enforces zero waste in the inventory system by always ensuring $S^* \leq eq$ where e is the deterministic expiration lifetime in days and q is the deterministic daily demand. With this upper bound on S^*, there may be instances where the maximum proportion of drug shortages constraint cannot be satisfied. When the maximum proportion of drug shortages constraint cannot be satisfied, the optimal inventory policy is always $(R^* = 1, S^* = eq)$ (i.e., the smallest R^* and the largest S^*) as this maximizes the expected inventory on-hand.

The (R, S) model assumes that the lead time is zero which is consistent with hospital pharmacies that tend to see very small lead times. The Central Pharmacy at the University of Michigan experiences lead times of 36-72 hours. Also, the model assumes orders can only be attempted at times that are integer multiples of R (regardless of the not disrupted versus disrupted status of the supply chain between review periods) and that orders are only successfully placed when the supply chain is not disrupted. This assumption implies that urgent orders (i.e., orders placed before the reordering period due to the hospital pharmacy exhausting all inventory) cannot be placed. However, we note that since the (R, S) model ensures that S covers at least one review period (i.e., $m \geq 1$; see Table 2), a hospital pharmacy would only exhaust all inventory before the reordering period if a supply chain disruption occurred. Given the lead time and integer multiples of R assumption, we can simply refer to inventory position as inventory on-hand. When applying the (R, S) model in this research, we assume that we have full and accurate knowledge of the inventory on-hand. Furthermore, we note that supply chain disruptions often last weeks, months, or years [3] which is much longer than the typical time between orders (i.e., R).

The (R, S) model assumes that supply chain disruptions follow a two-state supply process which is consistent with pharmaceutical supply chains [38, 39] (see figure illustrating the days to recovery after intervention); [40] (supply chain disruptions when time is modeled as continuous). A two-state supply process is modeled as a two-state discrete time Markov chain where the time the supply chain is in the not disrupted state is a geometric random variable with parameter $\alpha^{(1)}$ (i.e., disruption probability; mean up time of $\frac{1}{\alpha^{(1)}}$) and the time the supply chain is in the disrupted state is a geometric random variable with parameter $\beta^{(1)}$ (i.e., recovery probability; mean down time of $\frac{1}{\beta^{(1)}}$) [1]. A two-state supply process accounts for the duration of and time between supply chain disruptions. For perishability, the (R, S) model assumes that the medication has no quality decay [41] and has a deterministic lifetime that starts when the medication arrives at the pharmacy. Through discussions with our hospital pharmacy collaborators, we make this assumption because medications almost always arrive to the hospital pharmacy with at least two-thirds of their expiration lifetime remaining (e.g., when $e = 90$ days, a medication arrives to the pharmacy with an expiration lifetime of at least 60 days). Assuming that the remaining lifetime of the medication when it arrives to the pharmacy is stochastic leads to a more complicated analysis, but this analysis can be considered in future research. Also, the model assumes first-in-first-out protocols are in place which is consistent with practice at the University of Michigan's Central Pharmacy. For demand, the (R, S) model assumes that the daily demand, $q > 0$, is deterministic and static. For emphasis, our hospital pharmacy setting of interest does not have deterministic or static demand. In Section 3.2, we discuss how to use the (R, S) model in the adaptive framework to account for the real-world hospital pharmacy system that has stochastic and variable demand. We refer the reader to Appendix A.1 for a summary of the (R, S) model and implementation details.

3.1.1 Supply chain disruption parameters in the (R, S) model

In the (R, S) model, $\alpha^{(R)}$ and $\beta^{(R)}$ represent the supply chain disruption and recovery probability, respectively, for a review period of length R days. An important observation is that these values depend on the length of the review period R (i.e., a decision variable). Czerniak et al. [30] illustrate how to use the closed-form expressions to solve for the optimal (R^*, S^*) with only $\alpha^{(1)}$ and $\beta^{(1)}$ as input by leveraging $\mathbf{P}^{(i)}$ which is the i-step transition probability matrix (see Eq. 1; [42]).

$$\mathbf{P}^{(i)} = \begin{pmatrix} \cdot & \alpha^{(i)} \\ \beta^{(i)} & \cdot \end{pmatrix} = \begin{pmatrix} (1-\alpha^{(1)}) & \alpha^{(1)} \\ \beta^{(1)} & (1-\beta^{(1)}) \end{pmatrix}^{i} \tag{1}$$

In practice, we can find the values of $\alpha^{(1)}$ and $\beta^{(1)}$ by answering the following questions:

1. What proportion of the time is the medication short? Define this value as Q_1 ($Q_1 \in (0, 1)$; 0 implies never short and 1 implies always short).
2. If the medication goes short, how long do you think the shortage will last (in days)? Define this value as Q_2 ($Q_2 > 1$).

With $Q_2 > \frac{Q_1}{1-Q_1}$ (due to the (R, S) model requirement of $\alpha^{(R)} \leq \alpha^{(1)} < 1$; see Table 2) and $Q_2 > 1$ (due to the (R, S) model requirement of $\beta^{(R)} \leq \beta^{(1)} < 1$; see Table 2), we can solve for $\alpha^{(1)}$ and $\beta^{(1)}$ using the relation that $Q_1 = \frac{\alpha^{(1)}}{\alpha^{(1)}+\beta^{(1)}}$ and $Q_2 = \frac{1}{\beta^{(1)}}$. Here, Q_1 corresponds to the long-run probability that the supply chain is disrupted [43]. Using these equations, we have the results presented in Eqs. 2-3.

$$\alpha^{(1)} = \frac{Q_1}{Q_2(1-Q_1)} \tag{2}$$

$$\beta^{(1)} = \frac{1}{Q_2} \tag{3}$$

Through discussions with our hospital pharmacy collaborators, the value of Q_2 is very difficult to quantify in practice, but it is an important parameter as it defines $\alpha^{(1)}$ and $\beta^{(1)}$ in Eqs. 2 and 3, respectively. With this, the expression for the ratio of the expected proportion of drug shortages per day given a value Q_2 and the true value Q_2^* is provided in Czerniak [44].

3.2 Adapting the (R, S) inventory policy over time

We want to emphasize that in practice, contracts, logistics, and resources can make it challenging to update the (R, S) inventory policy very frequently (e.g., every day/week/month). A more common approach is updating the inventory policy when a problem arises (e.g., stockout; from discussions with our hospital pharmacy collaborators), and an easy approach is updating the inventory policy on fixed intervals like every 3 or 6 months (i.e., update every B days where $B \in \{90, 180\}$) where the average demand from the past B days is used to update the (R, S) inventory policy. We refer to this fixed interval approach as a benchmark inventory system. Unlike the benchmark inventory system that updates the inventory policy on long fixed intervals, we create an adaptive inventory system that endogenously detects when the (R, S) inventory policy needs to be updated at any point in time. We endogenously detect a change in the inventory policy is needed using a shortage threshold δ_s and waste threshold δ_w. These thresholds represent the change in the proportion of drug shortages per day and drugs wasted per

day, respectively, that the inventory system is willing to tolerate. Specifically, these thresholds guard against shortages when an increasing demand disruption and waste when a decreasing demand disruption occur, respectively. The shortage threshold δ_s and waste threshold δ_w are selected by a hospital pharmacy manager/administrator and in Section 5.2, we provide guidance and examples for the selection of these input parameters. When considering demand, as mentioned in Section 3.1, the (R, S) model assumes that demand is deterministic and static. However, our hospital pharmacy system of interest has stochastic and variable demand. For the deterministic aspect of the (R, S) model, we replace the deterministic daily demand (q) with the expected daily demand $(\bar{q}_{current})$ when solving for the (R, S) inventory policy; the term *current* implies that this expected daily demand defines the current (R, S) inventory policy. For the static aspect of the (R, S) model, we update this (R, S) inventory policy using a new expected daily demand $(\bar{q}_{new})$ when we endogenously detect a demand disruption.

We define the additional notation necessary for the adaptive inventory system in Table 3. We also present a depiction of how the adaptive demand parameters and estimates relate to one another in Fig. 1. We then proceed to define the expected proportion of drug shortages and drugs wasted per day for the (R, S) inventory system. We also explain how to endogenously detect when the inventory policy needs to be updated.

3.2.1 Expected proportion of drug shortages and drugs wasted per day

We proceed to present the closed-form expressions for the expected proportion of drug shortages per day and drugs wasted per day for a particular medication of interest. We use the closed-form expressions for these two proportions to detect when an inventory policy needs to be updated (see Section 3.2.2). To provide closed-form expressions for these two proportions, we assume that the daily demand is normally distributed. We consider the real-world unique training daily demand observations for the six 503B medications analyzed in the medication case study (see Section 5.4) when making this normality assumption. For each medication, the unique training daily demand observations consist of 56 daily demand observations when demand is not disrupted (see Section 5.1 for more details). For each medication, we consider the quantile-quantile plots (i.e., QQ-plots) and the Shapiro-Wilk test. We note that when applying the Shapiro-Wilk test (with a significance level 0.05) to the unique training daily demand observations for each medication, the real-world daily demand observations do not follow a normal distribution. However, we do not observe serious deviations from the normality assumption in the QQ-plots. Taking into account that the Shapiro-Wilk test is sensitive to even mild deviations from the normal distribution, we make the assumption that the daily demand is normally distributed. It is also worth noting that when there are concerns that the daily demand severely deviates from normality, transformations such as the Box-Cox transformation can be considered. For emphasis, we only use the normally distributed daily demand assumption for the derivation of the closed-form expressions. We use the real-world observed demand provided by the University of Michigan's Central Pharmacy throughout the other portions of the analysis.

Expected Proportion of Drug Shortages Per Day

Using the (R, S) model (see Section 3.1), Eq. 4 represents the expected proportion of drug shortages per day for a particular medication of interest when following a (R, S) inventory policy for an inventory system that has an expected daily demand of $\bar{q}$ (in Appendix B.1). Proportion is measured relative to the expected daily demand $\bar{q}$. From Eq. 4, the expected proportion of drug shortages per day depends on the length of the review period (R), the order-up-to level (S), the expected daily demand $(\bar{q})$, the disruption probability $(\alpha^{(R)})$, and the recovery probability $(\beta^{(R)})$. It is worth noting that the (R, S) policy is calculated using $\bar{q}_{current}$ which ensures that $m = \lfloor \frac{S}{\bar{q}_{current} R} \rfloor \geq 1$. However, with an expected daily demand of $\bar{q}$, the $m \geq 1$ requirement may no longer be satisfied which explains the two cases presented in Eq. 4. Furthermore, Czerniak et al. [30] illustrate that stochastic demand that is normally distributed has a negligible impact on the expected proportion of drug shortages per day with the (R, S) model. The reason for this finding is that the (R, S) model incorporates supply chain disruptions which encourage the inventory system to hold extra inventory on-hand. As a result, there is a negligible impact on the expected proportion of drug shortages per day when demand is stochastic. Hence, we simply consider a deterministic expected daily demand $\bar{q}$.

$$P_{short|(\bar{q},R,S)} = \tag{4}$$

$$\begin{cases} \frac{\alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m-1}}{(\alpha^{(R)}+\beta^{(R)})}\left(m+1-\frac{S}{\bar{q}R}\right)+\left(\frac{\alpha^{(R)}(1-\beta^{(R)})^{m}}{(\alpha^{(R)}+\beta^{(R)})}\right); \\ \quad \text{when } m \geq 1,\ m = \lfloor \frac{S}{\bar{q}R} \rfloor \\ \\ \frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}\left(\frac{\bar{q}R-S}{\bar{q}R}\right)+\left(1-\frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}\right); \\ \quad \text{when } m < 1,\ m = \lfloor \frac{S}{\bar{q}R} \rfloor \end{cases}$$

Table 3 Summary of the modeling notation for the adaptive inventory system

Notation	Description
Thresholds	
δ_s	Change in the proportion of drug shortages per day that signals a change in the (R, S) inventory policy when exceeded ($0 < \delta_s < 1$; input parameter)
δ_w	Change in the proportion of drugs wasted per day that signals a change in the (R, S) inventory policy when exceeded ($0 < \delta_w < 1$; input parameter)
Adaptive	
N	Number of past daily demand observations to consider for the adaptive inventory system daily demand estimates (input parameter)
q_t	Daily demand observed on day t (real-world hospital pharmacy data)
$\bar{q}_{current}$	Expected daily demand used for the current (R, S) policy
$\bar{q}_{new}$	Expected daily demand calculated using the average of the most recent N daily demand observations
σ_{new}	Standard deviation of daily demand calculated using the most recent N daily demand observations
$P_{short\|(\bar{q},R,S)}$	Expected proportion of drug shortages per day when following a (R, S) inventory policy for an inventory system that has an expected daily demand of $\bar{q}$
$P_{waste\|(\bar{q},\sigma,R,S)}$	Expected proportion of drugs wasted per day when following a (R, S) inventory policy for an inventory system that has an expected daily demand of $\bar{q}$ and standard deviation of daily demand σ
Benchmark	
B	Number of days the inventory system follows the same (R, S) inventory policy where the average of the last B days is used to update the inventory policy (input parameter)

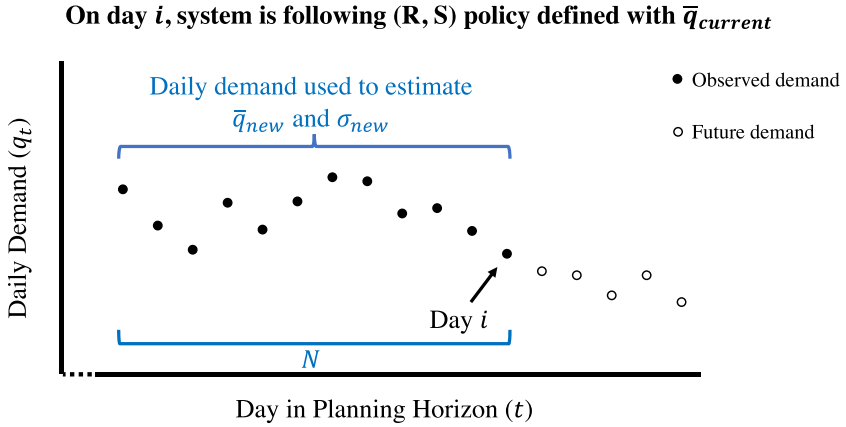


Fig. 1 Depiction of the adaptive demand parameters and estimates. $\bar{q}_{new}$ and σ_{new} are calculated at the end of day i after demand has been observed. If a demand disruption is endogenously detected at the end of day i, the new expected daily demand $\bar{q}_{new}$ is used to update the (R, S) inventory policy since the future demand has not yet been observed

$$P_{waste|(\bar{q},\sigma,R,S)} = \tag{5}$$

$$\begin{cases} \frac{E_w}{S}; & \lceil \frac{e}{R} \rceil = 1 \\ \frac{E_w}{(\lceil \frac{e}{R} \rceil R\bar{q} + E_w)\pi_0 + \sum_{j=\lceil \frac{e}{R} \rceil - 1}^{\infty} \pi_j (S + R\bar{q}(\frac{(\lceil \frac{e}{R} \rceil - 1)}{2}))}; & \lceil \frac{e}{R} \rceil = 2 \\ \frac{E_w}{(\lceil \frac{e}{R} \rceil R\bar{q} + E_w)(\pi_0 + \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} \pi_j - \frac{1}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j\pi_j) + \frac{S}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j\pi_j + \frac{R\bar{q}}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j^2\pi_j + \sum_{j=\lceil \frac{e}{R} \rceil - 1}^{\infty} \pi_j (S + R\bar{q}(\frac{(\lceil \frac{e}{R} \rceil - 1)}{2}))}; & \lceil \frac{e}{R} \rceil \geq 3 \end{cases}$$

where $E_w = \Big(S \cdot \Pr(Z < \frac{S - e\bar{q}}{\sqrt{e\sigma^2}}) - e\bar{q} - \frac{1}{2\pi} \Big(- e^{-\frac{(S-e\bar{q})^2}{2e\sigma^2}} + e^{-\frac{(-e\bar{q})^2}{2e\sigma^2}} \Big) \sqrt{e\sigma^2} \Big)$

Expected Proportion of Drugs Wasted Per Day

Equation 5 represents the expected proportion of drugs wasted per day for a particular medication of interest when following a (R, S) inventory policy for an inventory system that has an expected daily demand of $\bar{q}$ and standard deviation of daily demand σ (in Appendix B.2). Proportion is measured relative to the expected number of drugs ordered. To our knowledge, we are the first to present this value in closed-form. The expected proportion of drugs wasted per day in Eq. 5 depends on the length of the review period (R), the order-up-to level (S), the expected daily demand $(\bar{q})$, the standard deviation of daily demand (σ), the disruption probability ($\alpha^{(R)}$; in π_j), the recovery probability ($\beta^{(R)}$; in π_j), and the expiration lifetime (e). Z denotes a standard normal random variable and Appendix B.2 provides the closed-form expressions for the summations including π_j. π_j is the probability that the supply chain is disrupted for exactly j consecutive review periods ($\pi_0 = \frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}$; $\pi_j = \frac{\alpha^{(R)}\beta^{(R)}}{(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})}(1 - \beta^{(R)})^j, \quad j \geq 1$). Equation 5 accounts for stochastic demand where we assume that the daily demand is independent and normally distributed with mean $\bar{q}$ and standard deviation σ. Past research illustrates that the expected proportion of drugs wasted with the (R, S) model is sensitive to stochastic demand that is normally distributed, especially for medications with short expiration lifetimes.

3.2.2 Detecting when the inventory policy needs to be updated

On any day t, we follow a particular (R, S) inventory policy which is defined with respect to an expected daily demand of $\bar{q}_{current}$. In the presence of increasing and/or decreasing demand disruptions, we may need to update the inventory policy to avoid excessive drug shortages and/or drug waste. The key idea is that we consider how a shift in the expected daily demand impacts the expected proportion of drug shortages per day and expected proportion of drugs wasted per day. For the shift in the expected daily demand, we estimate the new expected daily demand $\bar{q}_{new}$ by averaging the most recent N daily demand observations and we compare this to $\bar{q}_{current}$; the expected daily demand used to define the current (R, S) inventory policy. We detect a change in the inventory policy is necessary if (a) $\bar{q}_{new} \geq \bar{q}_{current}$ and the shift in the expected daily demand causes the change in the expected proportion of drug shortages per day to exceed δ_s or (b) $\bar{q}_{new} < \bar{q}_{current}$ and the shift in the expected daily demand causes the change in the expected proportion of drugs wasted per day to exceed δ_w. If (a) or (b) holds, we update the (R, S) inventory policy using the new expected daily demand $\bar{q}_{new}$. It is worth noting that if $\bar{q}_{new} < \bar{q}_{current}$, the estimated standard deviation of demand (i.e., σ_{new}) will influence the expected proportion of drugs wasted per day as illustrated in Eq. 5. We illustrate an overview of the procedure in Fig. 2.

We proceed to describe the daily demand estimates and expected proportions needed for the adaptive inventory system. We then formally define the conditions that detect when the inventory policy needs to be updated.

Daily Demand Estimates and Expected Proportions

We estimate the expected daily demand $\bar{q}_{new}$ by averaging the most recent N daily demand observations. We initially considered other prediction approaches (e.g., ARIMA), but we found that a simple average approach performed just as well or better when considering the expected proportion of drug shortages per day and expected proportion of drugs wasted per day. We hypothesize that an averaging approach performs well due to the variable and noisy real-world daily demand data. We also found that knowing everything about the future (i.e., knowing the future N daily demand observations exactly) had a small or negligible impact on the performance. For medications with seasonal

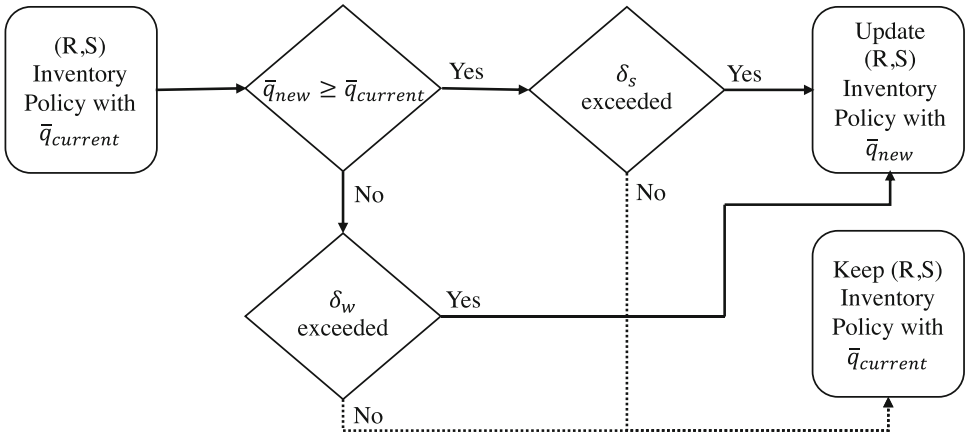


Fig. 2 Overview of the adaptive inventory system

data over a period of daily demand observations (e.g., demand is dependent on the day of the week), we suggest selecting N such that it is a multiple of the seasonal period (e.g., $N \in \{7, 14, 21, 28, 35, 42, 49, 56\}$ days for weekly seasonality). For medications that experience longer periods of seasonality (e.g., yearly), we note that the adaptive inventory system will endogenously detect changes in the demand over this longer period of time and appropriately update the (R, S) inventory policy. For the standard deviation of daily demand, we estimate the standard deviation of daily demand (i.e., σ_{new}) using the most recent N daily demand observations.

We first calculate the expected proportion of drug shortages per day when following a particular (R, S) inventory policy. We calculate this proportion for an inventory system that has an expected daily demand of $\bar{q}_{new}$ (i.e., $P_{short|(\bar{q}_{new},R,S)}$, see Eq. 4) which corresponds to the proportion estimate with the new demand mean. We also calculate this proportion for an inventory system that has an expected daily demand of $\bar{q}_{current}$ (i.e., $P_{short|(\bar{q}_{current},R,S)}$, see Eq. 4) which corresponds to the proportion estimate with the demand mean that defines the current (R, S) inventory policy. Next, we calculate the expected proportion of drugs wasted per day when following a particular (R, S) inventory policy. We calculate this proportion for an inventory system that has an expected daily demand of $\bar{q}_{new}$ and standard deviation of daily demand σ_{new} (i.e., $P_{waste|(\bar{q}_{new},\sigma_{new},R,S)}$, see Eq. 5) which corresponds to the proportion estimate with the new demand mean and new standard deviation of daily demand. We also calculate this proportion for an inventory system that has an expected daily demand of $\bar{q}_{current}$ and standard deviation of daily demand σ_{new} (i.e., $P_{waste|(\bar{q}_{current},\sigma_{new},R,S)}$, see Eq. 5) which corresponds to the proportion estimate with the demand mean that defines the current (R, S) inventory policy and new standard deviation of daily demand.

Conditions that Detect When the Inventory Policy Needs to Be Updated

Given $\bar{q}_{new} \geq \bar{q}_{current}$, we have an increase or no change in the expected daily demand. In this case, we compare $P_{short|(\bar{q}_{new},R,S)} - P_{short|(\bar{q}_{current},R,S)}$ to the shortage threshold δ_s; the change in the proportion of drug shortages per day that signals a change in the (R, S) inventory policy when exceeded. δ_s provides a numerical value to quantify the shortage concern. A smaller δ_s is recommended for medications that have a high shortage concern. We note that when $\bar{q}_{new} = \bar{q}_{current}$, $P_{short|(\bar{q}_{new},R,S)} - P_{short|(\bar{q}_{current},R,S)}$ will equal zero, but we include this scenario to simply break the analysis into two cases.

Given $\bar{q}_{new} < \bar{q}_{current}$, we have a decrease in the expected daily demand. In this case, we compare $P_{waste|(\bar{q}_{new},\sigma_{new},R,S)} - P_{waste|(\bar{q}_{current},\sigma_{new},R,S)}$ to the waste threshold δ_w; the change in the proportion of drugs wasted per day that signals a change in the (R, S) inventory policy when exceeded. δ_w provides a numerical value to quantify the waste concern. A smaller δ_w is recommended for medications that have a high waste concern.

Formally, the adaptive inventory system detects that the inventory policy needs to be updated if either condition in Eq. 6 is satisfied. We provide a detailed discussion on the selection of the input parameters δ_s and δ_w in Section 5.2.

$$\begin{cases} P_{short|(\bar{q}_{new},R,S)} - P_{short|(\bar{q}_{current},R,S)} > \delta_s; \\ \text{when } \bar{q}_{new} \geq \bar{q}_{current} \\ \\ P_{waste|(\bar{q}_{new},\sigma_{new},R,S)} - P_{waste|(\bar{q}_{current},\sigma_{new},R,S)} > \delta_w; \\ \text{when } \bar{q}_{new} < \bar{q}_{current} \end{cases} \tag{6}$$

Given we detect that the (R, S) inventory policy needs to be updated, we set $\bar{q}_{current} = \bar{q}_{new}$ and solve for the new (R, S) inventory policy using the (R, S) model.

$$P_{metric} = \begin{cases} \max\{0,\ P_{short|(\bar{q}_{new},R,S)} - P_{short|(\bar{q}_{current},R,S)} - \delta_s\}; & \text{when } \bar{q}_{new} \geq \bar{q}_{current} \\ \max\{0,\ P_{waste|(\bar{q}_{new},\sigma_{new},R,S)} - P_{waste|(\bar{q}_{current},\sigma_{new},R,S)} - \delta_w\}; & \text{when } \bar{q}_{new} < \bar{q}_{current} \end{cases} \quad (7)$$

3.3 Ranking medications

Managers at the University of Michigan's Central Pharmacy are responsible for making inventory decisions for 2,500+ medications. We create a ranking procedure to address the following questions:

1. Out of the 2,500+ medications, which (if any) medications should the hospital pharmacy be most concerned about?
2. If only a limited number of inventory policies can be updated, which medications (if any) should the hospital pharmacy focus on?

We present a ranking procedure that depends on the:

(a) fixed ordering cost for the medication (k)
(b) storage/holding cost for the medication (h)
(c) expiration lifetime of the medication (e)
(d) supply chain disruption profile of the medication ($\alpha^{(R)}$ and $\beta^{(R)}$)
(e) shortage concern (δ_s; change in the proportion of drug shortages per day that the decision-maker is willing to tolerate for the medication)
(f) waste concern (δ_w; change in the proportion of drugs wasted per day that the decision-maker is willing to tolerate for the medication)
(g) demand for the medication ($\bar{q}_{current}$ and $\bar{q}_{new}$)
(h) demand variability of the medication (σ_{new})

For the ranking procedure, we observe that the adaptive inventory system keeps a record of the change in the expected proportion of drug shortages per day and the change in the expected proportion of drugs wasted per day for a particular medication (see Eq. 6). We are interested in ranking the medications in order of decreasing concern. We introduce a proportion exceedance metric denoted P_{metric} which measures how much the shortage threshold δ_s is exceeded given $\bar{q}_{new} \geq \bar{q}_{current}$ and waste threshold δ_w is exceeded given $\bar{q}_{new} < \bar{q}_{current}$. We define P_{metric} in Eq. 7 where it is important to note that the adaptive inventory system only indicates that the (R, S) inventory policy needs to be updated when $P_{metric} > 0$.

P_{metric} encompasses characteristics (a)-(g). We rank the medications in order of decreasing concern by sorting the medications from largest to smallest using P_{metric}. There are multiple ways that decision-makers can implement the ranking procedure in practice (e.g., update medications based on P_{metric} every day, update medications based on the average value of P_{metric} over a fixed interval of days). In Section 5.5, we illustrate one way of implementing the ranking procedure in practice and we analyze the results.

4 Simulation models

With the varying drug shortage-waste weightings and supply chain disruption profiles, we use simulation modeling to assess the performance of multiple inventory systems. We create simulation models of four inventory systems: (A) Adaptive Inventory System (in Section 4.1), (B) Adaptive with Buyback Inventory System (in Section 4.2), (C) Benchmark Inventory System (in Section 4.3), and (D) Static Inventory System (in Section 4.3). We let t denote the day in the planning horizon where the decision-maker can select the initialization of t. We let r denote the number of days remaining in the review period until the next order is attempted, b denote the number of days since the (R, S) inventory policy has been updated, I_i denote the inventory on-hand with a lifetime remaining of i days ($i = 1, ..., e$), and I_{tot} denote the total inventory on-hand. To assess the performance of the system, we record the number short each day t (i.e., $short_t$), the number wasted each day t (i.e., $waste_t$), the number held each day t (i.e., h_t), and the number successfully ordered each day t (i.e., o_t).

4.1 (A) Adaptive inventory system

Ignoring the bold text, Fig. 3 provides a step-by-step description of the simulation model representing a periodic review inventory system with adaptive inventory policies. To initialize the model, we (a) define $\bar{q}_{current}$ using the first B daily demand observations and solve for the optimal (R^*, S^*)

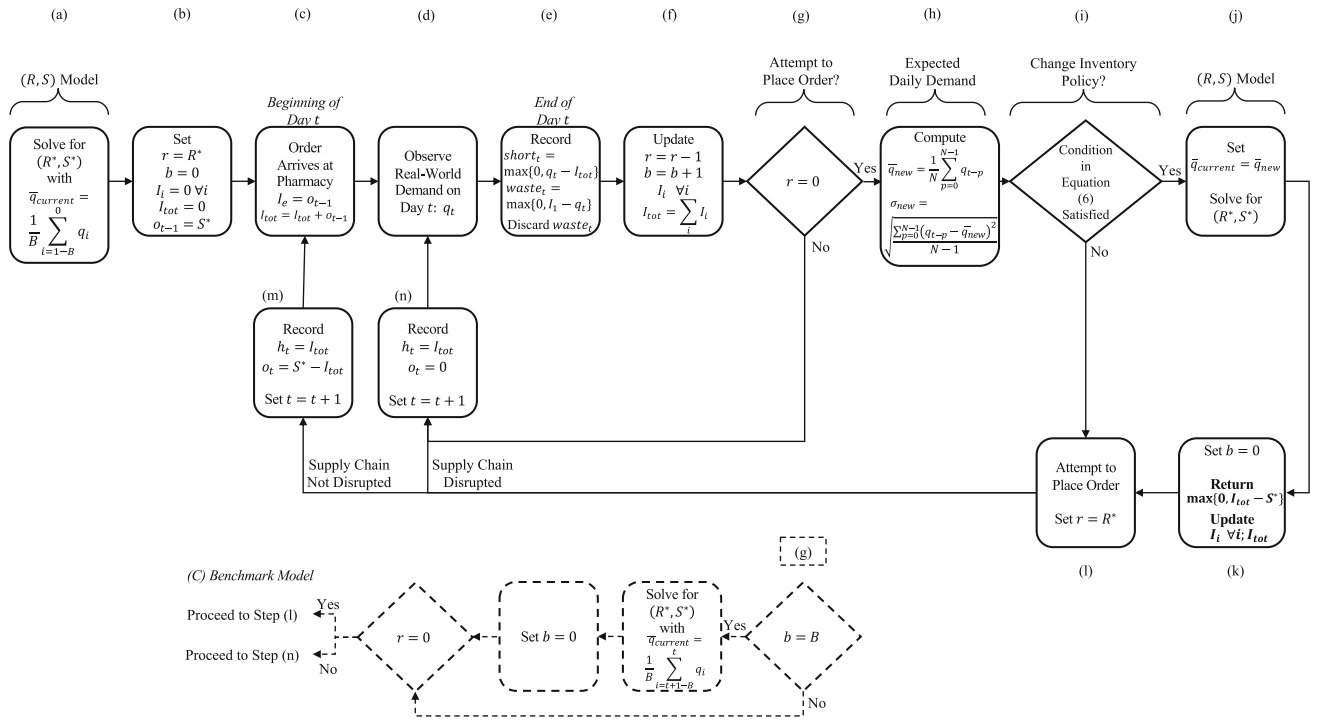


Fig. 3 Simulation model road map for the (A) Adaptive, (B) Adaptive with Buyback, and (C) Benchmark inventory systems. For (A), follow steps (a)-(n) and omit the bold text. For (B), follow steps (a)-(n) and implement the bold text to incorporate buyback. For (C), starting at step (g), replace the process with the dashed shapes/lines

inventory policy. We then (b) initialize $r = R^*$ (i.e., there are R^* days remaining in the review period until an order should be attempted), $b = 0$ (i.e., it has been 0 days since the inventory policy has been updated), $I_i = 0 \quad \forall i = 1, ..., e$ (i.e., the inventory system has zero inventory on-hand across all lifetimes), $I_{tot} = 0$ (i.e., the total inventory on-hand is zero), and $o_{t-1} = S^*$ (i.e., S^* drugs will arrive on day t).

After initializing the model, an iterative procedure begins. At the beginning of day t, (c) an order placed on day $t-1$ arrives at the hospital pharmacy (when supply is not disrupted) recalling the (R, S) model zero lead time assumption. The inventory levels are appropriately updated. Then, we (d) observe the real-world daily demand (i.e., q_t). At the end of day t, we (e) record the number of drug shortages on day t (i.e., $short_t$), record the number of drugs wasted on day t (i.e., $waste_t$), and discard these wasted drugs. Then, we (f) subtract one day from the number of days remaining in the review period (i.e., $r = r - 1$), add one day to the number of days since the inventory policy has been updated (i.e., $b = b + 1$), and appropriately update the inventory levels. Then, (g) if $r = 0$ (i.e., there are zero days remaining in the review period), an order should be attempted. Thus, we proceed to step (h). Otherwise, no order attempt is necessary so we (n) record the number of drugs held (i.e., $h_t = I_{tot}$) and ordered (i.e., $o_t = 0$) on day t, and start the process back at step (d).

Given an order should be attempted, we (h) use the most recent N daily demand observations to estimate the expected daily demand $\bar{q}_{new}$ and standard deviation of daily demand σ_{new}. Then, we (i) determine if the (R, S) inventory policy needs to be updated by seeing if either condition in Eq. 6 is satisfied (i.e., $\bar{q}_{new} \geq \bar{q}_{current}$ & $P_{short|(\bar{q}_{new}, R^*, S^*)} - P_{short|(\bar{q}_{current}, R^*, S^*)} > \delta_s$ or $\bar{q}_{new} < \bar{q}_{current}$ & $P_{waste|(\bar{q}_{new}, \sigma_{new}, R^*, S^*)} - P_{waste|(\bar{q}_{current}, \sigma_{new}, R^*, S^*)} > \delta_w$). If the (R, S) inventory policy needs to be updated, we (j) update the inventory policy by setting $\bar{q}_{current} = \bar{q}_{new}$ and solve for the corresponding optimal (R^*, S^*) inventory policy. After step (j), we (k) set $b = 0$ to indicate that it has been zero days since the inventory policy has been updated. Finally, we (l) attempt to place an order based on the (R^*, S^*) inventory policy and set $r = R^*$. When supply is not disrupted, the order is successful. We (m) record the number of drugs held (i.e., $h_t = I_{tot}$) and ordered (i.e., $o_t = S^* - I_{tot}$) on day t, and start the process back at step (c). When supply is disrupted, the order is unsuccessful. We (n) record the number of drugs held (i.e., $h_t = I_{tot}$) and ordered (i.e., $o_t = 0$) on day t, and start the process back at step (d).

4.2 (B) Adaptive inventory system with buyback

Through discussions with our hospital pharmacy collaborators at the University of Michigan's Central Pharmacy, some

contracts allow the pharmacy to return drugs if the hospital pharmacy has too much inventory on-hand. With these buyback programs in mind, we create a simulation model of a periodic review inventory system with adaptive inventory policies where the hospital pharmacy can return drugs to the supplier given the inventory on-hand exceeds the optimal order-up-to level S^*. Taking notice to the bold text, Fig. 3 presents the step-by-step description of the simulation model. We add an extra operation (see bold text) in step (k) where we allow the hospital pharmacy to return all drugs that cause the inventory on-hand to exceed the optimal order-up-to level S^*. We assume that the newest inventory (i.e., longest remaining lifetime) is returned and that the hospital pharmacy receives full compensation for the returned drugs.

4.3 (C) Benchmark inventory system and (D) static inventory system

The simulation model for the benchmark inventory system and static inventory system is the same as the adaptive inventory system (i.e., (A) Adaptive) except the (R, S) inventory policy is only updated when $b = B$ (see dashed shapes/lines in Fig. 3) and the (R, S) inventory policy is never updated, respectively.

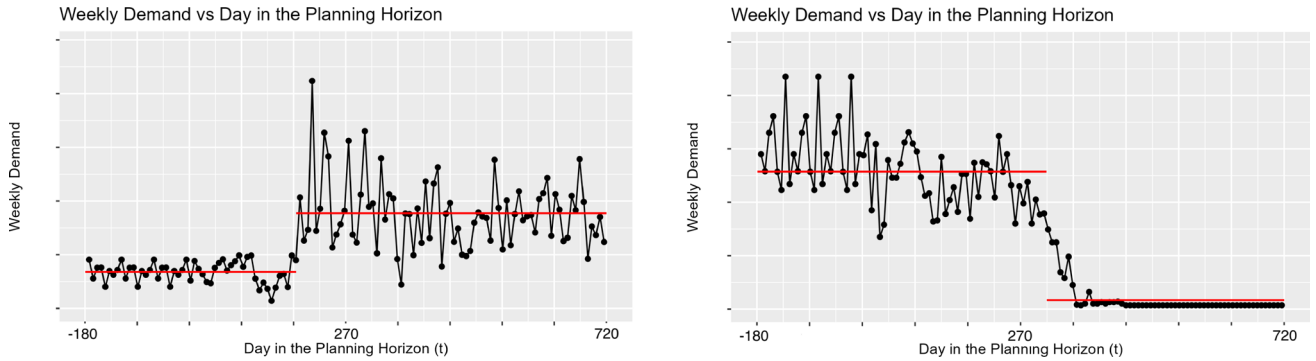
5 Numerical analysis

We use daily demand data from the University of Michigan's Central Pharmacy (October 2019-November 2021). This two year period captures demand before the Covid-19 pandemic and fluctuations in demand during the Covid-19 pandemic. We analyze how a medication's shortage-waste weighting and supply chain disruption profile influence the benefits (or detriments) of adapting to demand disruptions. We present the data (in Section 5.1), shortage-waste weightings (in Section 5.2), and input parameters (in Section 5.3). We proceed to study the benefits (or detriments) of adapting to demand disruptions in Section 5.4. Then, we analyze the ranking procedure (see Section 3.3) in Section 5.5. Throughout the numerical analysis, we denote days $t \leq 0$ as the training horizon and days $t > 0$ as the testing horizon. Also, the (R, S) model treats R and S as continuous decision variables. We take a conservative approach by rounding R down to the nearest whole number and S up to the nearest whole number. For all other computations that require an integer value, we round to the nearest whole number (e.g., $\bar{q}_{current}$). We also ensure that all daily demand values are positive as the (R, S) model requires a positive daily demand ($\bar{q}_{current} > 0$) and demand is always non-negative in practice.

5.1 Real-world data

The Central Pharmacy at the University of Michigan manages and keeps records for 2,500+ medications (e.g., surgical, cancer, daily care for inpatients). Except when analyzing the ranking procedure (in Section 5.5), we focus on 503B medications which are pre-compounded medications that arrive to the pharmacy in ready-to-use presentations ([45]; see *Stability in the Supply Chain* at https://www.fagronsterile.com/newsroom/what-is-a-503b-compounding-pharmacy). If a 5 03B medication experiences a shortage, hospital pharmacies will often substitute the medication with the form that requires compounding before administration. This form of the medication requires additional pharmacy resources and has a very small expiration lifetime once compounded (e.g., 24 hours). If a 503B medication is wasted due to expiration, hospital pharmacies experience a higher waste cost because a 503B medication is often more expensive than the form that requires compounding before administration. There is also an increased chance of drug waste with 503B medications because 503B medications have fairly short expiration lifetimes (e.g., 90 days) in comparison to non-503B medications (e.g., $\geq$ 360 days; for medications that require compounding, referring to the expiration lifetime of the product before it is compounded). These are additional reasons why it is critical to avoid drug shortages and drug waste for this class of medications.

We start by analyzing two 503B medications. The first medication is (a) Rocuronium 10 mg/1mL (Rocuronium) which is a paralyzing agent that is critical to have on-hand and is most often used for rapid sequence intubation. The second medication is (b) Labetalol 5mg/1mL (Labetalol) which is a critical medication used for blood pressure reduction for several indications. Figure 4 presents the weekly demand where the red horizontal lines denote the corresponding mean weekly demand that minimizes the sum of squared errors for the daily demand data. It is worth noting that the red horizontal lines for Rocuronium resemble an increasing demand disruption and the red horizontal lines for Labetalol resemble a decreasing demand disruption. Furthermore, for both Rocuronium and Labetalol, the two groups of daily demand observations corresponding to the red horizontal lines are statistically different at a 0.05 significance level when applying a non-parametric Mann Whitney U test to the two groups. Through discussions with our hospital pharmacy collaborators, the demand disruptions for Rocuronium and Labetalol are a result of changes in the patient population during the Covid-19 pandemic (e.g., cancellation of elective surgeries). The training horizon (i.e., $t \leq 0$) consists of the first 56 unique daily demand observations (8 weeks) stacked four



(a) Rocuronium. (b) Labetalol.

Fig. 4 Weekly demand versus day in the planning horizon. Numerical values are removed on the y-axis for data confidentiality

times (i.e., demand observation 1, 2,..., 56, 1, 2,..., 56, 1, 2,..., 56, 1, 2,..., 56) to have 224 observations. Then, we only select observations $45 - 224$ to obtain 180 daily demand training observations (i.e., about 6 months). We replicate and stack these daily demand observations when constructing the training data set to have a training data set that is not impacted by the Covid-19 pandemic. Beyond Rocuronium and Labetalol, we consider four additional 503B medications at the end of Section 5.4.

5.2 Shortage-waste weighting

A medication's shortage-waste weighting defines the shortage concern (defined by δ_s) and waste concern (defined by δ_w) for a particular medication of interest. This input parameter is selected by a hospital pharmacy manager/administrator. Working closely with our hospital pharmacy collaborators, we study a range of (δ_s, δ_w) values such that $\delta_s + \delta_w = 0.1$ where $\delta_s \in [0.01, 0.09]$ and $\delta_w \in [0.01, 0.09]$ to capture the trade-off between these two measures. In the following section, we select $\gamma = 0.05$. This implies that the (R, S) model ensures that shortages occur 5% of the time given the shortage constraint can be satisfied in the (R, S) model (see Section 3.1). Therefore, our range of $\delta_s \in [0.01, 0.09]$ values detects when shortages occur more than $6\% - 14\%$ of the time, respectively. It is important to note that a shift from 5% of the time to 6% of the time is a 20% increase in shortages. Also, the adaptive inventory system considers the percentage of drugs wasted with the mean demand used to define the current (R^*, S^*) inventory policy (i.e., $100 * P_{waste|(\bar{q}_{current}, \sigma_{new}, R^*, S^*)}\%$) and the new mean demand (i.e., $100 * P_{waste|(\bar{q}_{new}, \sigma_{new}, R^*, S^*)}\%$) given a standard deviation of daily demand σ_{new}. Therefore, our range of $\delta_w \in [0.01, 0.09]$ values detects when the difference in the percentage of drugs wasted is more than $1\% - 9\%$, respectively. Figure 5 illustrates a medication's shortage-waste weighting where we also provide medication examples in black *italics*. We note that when $(\delta_s, \delta_w) = (0.05, 0.05)$, the model is equally sensitive to changes in drug shortages and drug waste. We also note that for medications with a very high shortage concern, a hospital pharmacy manager/administrator can select a shortage-waste weighting with a high shortage concern and low waste concern (e.g., $(\delta_s, \delta_w) = (0.01, 0.09)$) and couple this with a small proportion of demand not satisfied for the (R, S) model (e.g., $\gamma = 0.01$).

5.3 Model input parameters

We provide a summary of the input parameters for the numerical analysis in Table 4. For the (R, S) model, through discussions with our hospital pharmacy collaborators, we estimate the ordering cost (k) using 10 times the cost of the medication (i.e., $k = 10 \cdot$(medication price)). We consider a daily holding cost (h) relative to medication price of 0.001 (i.e., $h = 0.001 \cdot$(medication price); [46]). Through discussions with our hospital pharmacy collaborators, Rocuronium and Labetalol have a wholesale price of about \$12 and \$7 per dose, respectively. Furthermore, by discussing with our hospital pharmacy collaborators, we consider an expiration lifetime of 90 days (i.e., $e = 90$) which is consistent with the class of 503B medications. When solving for the optimal (R^*, S^*) policy, we constrain shortages to occur only 5% of the time (i.e., $\gamma = 0.05$). Also, when modeling supply chain disruptions as a two-state discrete time Markov chain (see Section 3.1), we consider four supply chain disruption profiles, $(\alpha^{(1)}, \beta^{(1)}) = \{(\frac{1}{30}, \frac{1}{10}), (\frac{1}{90}, \frac{1}{30}), (\frac{1}{270}, \frac{1}{90}), (\frac{1}{810}, \frac{1}{270})\}$, where $\frac{1}{x}$ corresponds to an expected duration of x days. Our hospital pharmacy collaborators at the University of Michigan have observed a variety of supply chain disruption lengths in practice (e.g., 1-3 months and 8-9 months). These $(\alpha^{(1)}, \beta^{(1)})$ supply chain disruption profiles all have the same long-run probability that the supply chain is disrupted: $\frac{\alpha^{(1)}}{\alpha^{(1)}+\beta^{(1)}} = 0.25$. Demand for

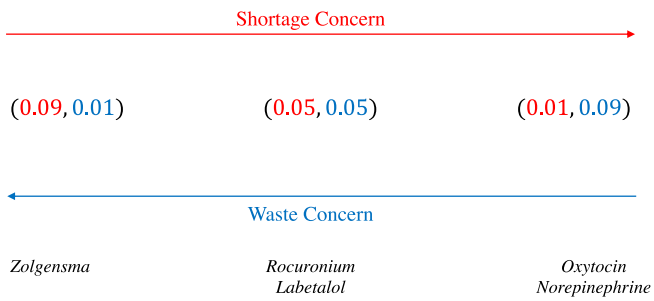


Fig. 5 A medication's shortage-waste weighting. From left to right, the concern for shortages increases (i.e., δ_s decreases) and the concern for waste decreases (i.e., δ_w increases)

a medication often depends on the day of the week, so we consider $N = 56$ past daily demand observations when estimating the expected daily demand and standard deviation of daily demand for the adaptive inventory system (i.e., 56 is divisible by 7). We provide additional details and suggestions for the selection of N in Section 5.6. We consider a benchmark inventory system that follows the same inventory policy for $B = 90$ days (i.e., about 3 months).

For all simulation models, we initialize $\bar{q}_{current}$ using the first $B = 90$ training daily demand observations as shown in Section 4. However, to warm-up the simulation model, we replicate and stack the entire set of 180 training daily demand observations 4 times to have a total warm-up period of 4(180) days (i.e., $\approx$ 2 years). Following the warm-up period, we always consider a testing horizon of 720 days (i.e., $\approx$ 2 years). We first note that we consider a long warm-up period to ensure that the inventory on-hand is appropriately balanced across the potential lifetimes of the medication (i.e., not all of the inventory on-hand is "new"). Also, a sufficient warm-up period coupled with 1,000 simulation replications makes it likely that all possible supply chain disruption patterns are well represented. We specifically select 1,000 simulation replications as this ensures a 95% confidence interval half-width of at most 0.01 for the proportion of drug shortages per day for Rocuronium and Labetalol with the (A) Adaptive model when $(\delta_s, \delta_w) = (0.05, 0.05)$ and $(\alpha^{(1)}, \beta^{(1)}) = (\frac{1}{270}, \frac{1}{90})$.

For the adaptive models (i.e., (A) Adaptive and (B) Adaptive with Buyback), we use the most recent $N = 56$ daily demand observations to endogenously detect demand disruptions and update the (R, S) inventory policy. It is worth noting that we initialize all the simulation models using the

Table 4 Numerical analysis input parameters

Notation	Description
Input parameters	
$k = 10$·(medication price)	Fixed ordering cost (i.e., for each order attempted)
$h = 0.001$·(medication price)	Holding cost per day per drug
$e = 90$	Expiration lifetime in days
$\gamma = 0.05$	Maximum proportion of drug shortages per day over the infinite horizon
$\alpha^{(1)} \in \{\frac{1}{30}, \frac{1}{90}, \frac{1}{270}, \frac{1}{810}\}$	Supply chain disruption probability with respect to 1 day
$\beta^{(1)} \in \{\frac{1}{10}, \frac{1}{30}, \frac{1}{90}, \frac{1}{270}\}$	Supply chain recovery probability with respect to 1 day
$\delta_s \in [0.01, 0.09]$	Change in the proportion of drug shortages per day that signals a change in the (R, S) inventory policy when exceeded
$\delta_w \in [0.01, 0.09]$	Change in the proportion of drugs wasted per day that signals a change in the (R, S) inventory policy when exceeded
$N = 56$	Number of past daily demand observations to consider for the adaptive inventory system daily demand estimates
$B = 90$	Number of days the inventory system follows the same (R, S) inventory policy where the average of the last B days is used to update the inventory policy
Warm-up= 4(180)	Length of the warm-up period in days for the simulation models
Reps= 1, 000	Number of simulation replications

first $B = 90$ training daily demand observations which keeps consistency across all four inventory systems of interest: (A) Adaptive, (B) Adaptive with Buyback, (C) Benchmark, and (D) Static. Furthermore, we implement a long warm-up period that uses the first 180 training daily demand observations stacked 4 times for the simulation models (i.e., ≈ 2 years). But, the sole purpose of consistent initialization and long warm-up periods is to compare the performance of the systems without bias. When implementing these inventory systems in practice, the (A) Adaptive and (B) Adaptive with Buyback inventory systems only require N daily demand observations for initialization. The (C) Benchmark inventory system only requires B daily demand observations for initialization. The (D) Static inventory system only requires N or B daily demand observations (based on the decision-maker) for initialization.

5.4 Medication case studies

We proceed to present the results for the medication case studies. Specifically, we provide the results for (a) Rocuronium and (b) Labetalol. At the end of this section, we consider four additional 503B medications and summarize the results in a table. For all analyses, we use the real-world demand data provided by the Central Pharmacy at the University of Michigan and we simulate the performance of the (A) Adaptive, (B) Adaptive with Buyback, (C) Benchmark, and (D) Static models. For clarity, from a shortage perspective, we claim that adaptive inventory policies are beneficial if the adaptive model (e.g., (A) Adaptive and (B) Adaptive with Buyback) leads to a smaller proportion of drug shortages per day in comparison to the (D) Static model. We claim that adaptive inventory policies are detrimental if the adaptive model has a larger proportion of drug shortages per day in comparison to the (D) Static model. From a waste perspective, we claim that adaptive inventory policies are beneficial if the adaptive model (e.g., (A) Adaptive and (B) Adaptive with Buyback) leads to a smaller proportion of drugs wasted per day in comparison to the (D) Static model. We claim that adaptive inventory policies are detrimental if the adaptive model has a larger proportion of drugs wasted per day in comparison to the (D) Static model. We also provide additional insights using the (C) Benchmark model.

5.4.1 Rocuronium and labetalol case studies

We present the results for Rocuronium (see Fig. 6) and Labetalol (see Fig. 7). We present the overall expected proportion of drug shortages per day and proportion of drugs wasted per day over the testing horizon. The testing horizon is 720 days (i.e., ≈ 2 years). We also present the expected number of inventory policy changes made over the course of the testing horizon. For the shortage-waste weightings (see x-axis in Figs. 6 and 7), we consider $\delta_w \in [0.01, 0.09]$ such that $\delta_s + \delta_w = 0.1$. For the supply chain disruption profile, we focus on supply chain disruptions with an expected duration of 90 days: $(\alpha^{(1)}, \beta^{(1)}) = (\frac{1}{270}, \frac{1}{90})$. Also, for the supply chain disruption profile, we provide the disruption probability with respect to 1 day (i.e., $\alpha^{(1)}$), recovery probability with respect to 1 day (i.e., $\beta^{(1)}$), and optimal (R^*, S^*) inventory policy when the mean of the first $B = 90$ training daily demand observations (i.e., initial $\bar{q}_{current}$) are used for the expected daily demand $\bar{q}_{current}$ (see Fig. 3 step (a)).

From Figs. 6 and 7, we find that (a) for a fixed supply chain disruption profile, a medication's shortage-waste weighting dictates the magnitude of the benefits (or detriments) of adaptive inventory policies. For example, consider the proportion of drugs wasted per day for Rocuronium (see Fig. 6 column 2). When the model is more concerned with shortages implying δ_w is large since $\delta_w + \delta_s = 0.1$ (see x-axis), the detriments of an adaptive model (i.e., (A) Adaptive and (B) Adaptive with Buyback) in comparison to the static model (i.e., (D) Static) are greater than a model that is more concerned with waste implying δ_w is small. We note that the (D) Static model always performs well in terms of the proportion of drugs wasted. We most likely observe this because Rocuronium resembles an increasing demand disruption (see Fig. 4(a)). The (D) Static model never changes the inventory policy when the increase in demand occurs implying the (D) Static model is always under-ordering. As a result, the (D) Static model performs well from a waste perspective (see Fig. 6 column 2), but not a shortage perspective (see Fig. 6 column 1). Consider the proportion of drugs wasted per day for Labetalol (see Fig. 7 column 2). When the model is more concerned with shortages implying δ_w is large (see x-axis), the benefits of an adaptive model (i.e., (A) Adaptive and (B) Adaptive with Buyback) in comparison to the static model (i.e., (D) Static) are slightly less than a model that is more concerned with waste implying δ_w is small. We note that the (D) Static model always performs well in terms of the proportion of drugs shortages. We most likely observe this because Labetalol resembles a decreasing demand disruption (see Fig. 4(b)). The (D) Static model never changes the inventory policy when the decrease in demand occurs implying the (D) Static model is always over-ordering. As a result, the (D) Static model performs well from a shortage perspective (see Fig. 7 column 1), but not a waste perspective (see Fig. 7 column 2).

Selecting a shortage-waste weighting with a high shortage [waste] concern often performs better than a shortage-waste weighting with a low shortage [waste] concern with respect to the proportion of drug shortages [drugs wasted] per day. However, it is worth noting that we do not always observe a monotone property for the proportion of drug shortages per day and the proportion of drugs wasted per day as we vary (δ_s, δ_w). For example, consider the proportion of

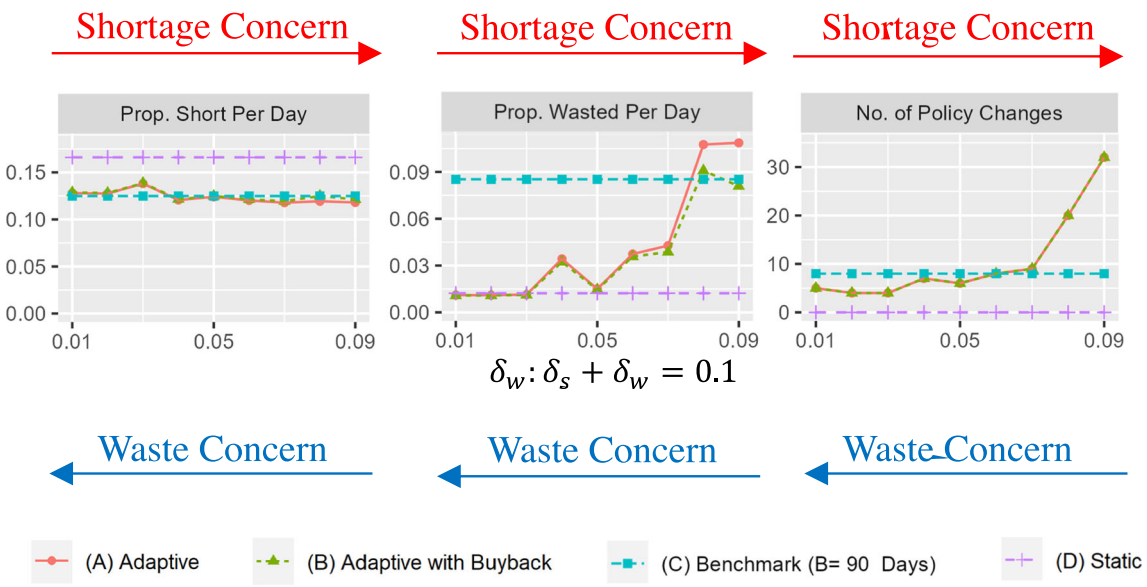


Fig. 6 Rocuronium results with models (A)-(D). We consider long supply chain disruption durations where $\alpha^{(1)} = \frac{1}{270}$ and $\beta^{(1)} = \frac{1}{90}$. We have that $(R^*, S^*) = (1, 8910)$ with an initial $\bar{q}_{current} = 98$. The x-axis illustrates δ_w such that $\delta_w + \delta_s = 0.1$ implying δ_w increases from left to right and δ_s decreases from left to right. Recall that δ_w and δ_s represent the change in the proportion of drugs wasted per day and drug shortages per day that the inventory system is willing to tolerate. See Fig. 4(a) for the observed demand over the planning horizon

drugs wasted per day for Rocuronium (see Fig. 6 column 2). There are instances where a shortage-waste weighting that is less concerned with waste (e.g., $\delta_w = 0.05$) has a smaller proportion of drugs wasted per day in comparison to a shortage-waste weighting that is more concerned with waste (e.g., $\delta_w = 0.04$). Taking a deeper look, we also find that the 95% confidence intervals around the point estimates for the proportion of drugs wasted per day for $\delta_w = 0.04$ and $\delta_w = 0.05$ do not intersect. However, it is important to note that the difference in the expected proportion of drugs wasted per day with $\delta_w = 0.04$ and $\delta_w = 0.05$ is very small (i.e., difference of 0.019). Furthermore, if we consider all

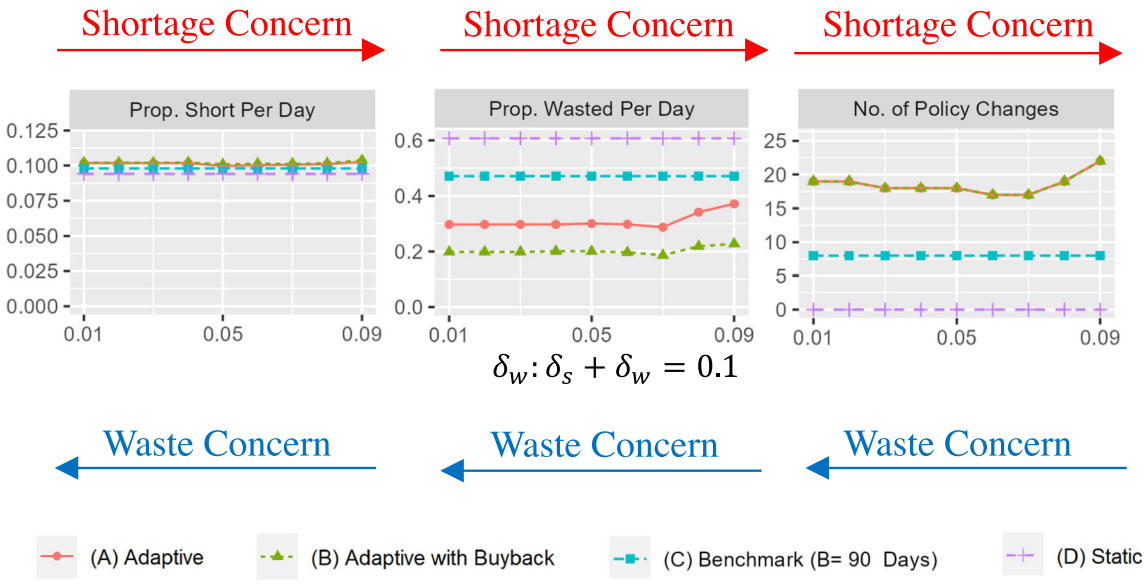


Fig. 7 Labetalol results with models (A)-(D). We consider long supply chain disruption durations where $\alpha^{(1)} = \frac{1}{270}$ and $\beta^{(1)} = \frac{1}{90}$. We have that $(R^*, S^*) = (1, 3780)$ with an initial $\bar{q}_{current} = 43$. The x-axis illustrates δ_w such that $\delta_w + \delta_s = 0.1$ implying δ_w increases from left to right and δ_s decreases from left to right. Recall that δ_w and δ_s represent the change in the proportion of drugs wasted per day and drug shortages per day that the inventory system is willing to tolerate. See Fig. 4(b) for the observed demand over the planning horizon

non-monotone instances across the six 503B medications of interest in this research, we continue to find a very small difference in the expected proportion of drug shortages per day or drugs wasted per day (i.e., difference ≤ 0.03). From a practical perspective, these very small differences may not be significant. We suspect that these non-monotone instances are a combination of (1) simulation sampling error and (2) the medication shortage concern (i.e., δ_s) and medication waste concern (i.e., δ_w) causing small differences on when an inventory policy is updated and the frequency of an inventory policy being updated.

When looking at the number of policy changes, we find that (b) the number of policy changes with the (A) Adaptive and (B) Adaptive with Buyback models is largely influenced by the medication shortage concern (i.e., δ_s) and medication waste concern (i.e., δ_w). Consider the number of policy changes for Rocuronium (see Fig. 6 column 3). As the model becomes more concerned with shortages (i.e., δ_w increases), the number of policy changes generally increase. Consider the number of policy changes for Labetalol (see Fig. 7 column 3). The number of policy changes is fairly stable for the multiple (δ_s, δ_w) shortage-waste weightings. But, the number of policy changes starts to increase as the model becomes more concerned with shortages.

We next take a deeper look at the (C) Benchmark model which updates the inventory policy every $B = 90$ days using the average daily demand from the most recent $B = 90$ days. In the upcoming Section 5.6, we emphasize that (c) the (C) Benchmark model can lead to very poor performance. If we consider Figs. 6 and 7, we can start to see this finding. The proportion of drug shortages per day with the (A) Adaptive, (B) Adaptive with Buyback, and (C) Benchmark models are very similar. But, the proportion of drugs wasted per day with the (C) Benchmark model is much greater than the proportion of drugs wasted per day with the (A) Adaptive and (B) Adaptive with Buyback models for almost all shortage-waste weightings.

We also find that (d) when considering the proportion of drugs wasted per day particularly for a medication that resembles a decreasing demand disruption (e.g., Labetalol; see Fig. 4(b)), the (B) Adaptive with Buyback model outperforms the (A) Adaptive model (see Fig. 7 column 2). Recall that the (B) Adaptive with Buyback model allows the hospital pharmacy to return drugs when the order-up-to level S^* is less than the inventory on-hand. The improvement in the proportion of drugs wasted per day with zero to negligible impact on the proportion of drug shortages per day encourages the use of such buyback programs. Furthermore, when considering a medication that resembles a decreasing demand disruption, an inventory policy that stocks a lot of inventory on-hand (i.e., a large order-up-to level S; e.g., a medication with a long expected duration of supply disruptions) may see great benefits from a buyback program in terms of the expected proportion of drugs wasted.

5.4.2 Other medications of interest and statistical significance

In addition to Rocuronium and Labetalol, we summarize the results (see Table 5) for four other 503B medications of interest: Avastin 1.25mg/0.05mL (chemotherapy with several indications; wholesale price of about $55 per dose), Oxytocin 30 units/500mL (induction of labor; wholesale price of about $10 per dose), Cefazolin 2gm/100mL (antibiotic; wholesale price of about $14 per dose), Norepinephrine 16mg/250mL (vasopressor used to increase blood pressure; wholesale price of about $25 per dose). The wholesale prices were obtained through discussions with our hospital pharmacy collaborators. The weekly demand data are provided in Appendix C.1. Like Rocuronium and Labetalol (see Section 5.1), through discussions with our hospital pharmacy collaborators, the demand disruptions for Avastin, Oxytocin, Cefazolin, and Norepinephrine are a result of changes in the patient population during the Covid-19 pandemic. In Table 5, we present the ratio of the proportion of drug shortages per day with the (D) Static model to the proportion of drug shortages per day with the (A) Adaptive model for varying shortage-waste weightings and supply chain disruption profiles. We present the ratio to the hundredths place. A ratio that is greater than 1 implies that the (A) Adaptive model is beneficial (i.e., decreases the proportion of drug shortages per day) and a ratio that is less than 1 implies that the (A) Adaptive model is detrimental (i.e., increases the proportion of drug shortages per day). We do the same for the proportion of drugs wasted per day. Numbers with asterisks indicate that the proportion with the (A) Adaptive model and (D) Static model are statistically different at a 0.05 (*) and 0.01 (**) significance level when applying a non-parametric Wilcoxon signed-rank paired test to the 1,000 simulation replications. Furthermore, when the proportion with the (A) Adaptive model or (D) Static model is zero, we present the difference between the two proportions (i.e., (A) Adaptive - (D) Static) and indicate this with a "D" before the numerical value.

In Table 5, we present three shortage-waste weightings: $(\delta_s, \delta_w) \in \{(0.075, 0.025), (0.05, 0.05), (0.025, 0.075)\}$. When viewing Table 5, we note that the medication shortage concern increases and the medication waste concern decreases when viewing the shortage-waste weightings from left to right. In Table 5, when modeling supply chain disruptions as a two-state discrete time Markov chain (see Section 3.1), we present four supply chain disruption profiles: $(\alpha^{(1)}, \beta^{(1)}) = \{(\frac{1}{30}, \frac{1}{10}), (\frac{1}{90}, \frac{1}{30}), (\frac{1}{270}, \frac{1}{90}), (\frac{1}{810}, \frac{1}{270})\}$. All of the supply chain disruption profiles have the same long-run probability that the supply chain is disrupted (i.e.,

Table 5 Case study results for all 503B drugs of interest

$(\alpha^{(1)}, \beta^{(1)})$	Disruption Duration Description	δ_s, δ_w (0.075, 0.025) more concerned with waste		(0.05, 0.05)		(0.025, 0.075) more concerned with shortages	
		Shortage Ratio	Waste Ratio	Shortage Ratio	Waste Ratio	Shortage Ratio	Waste Ratio
Rocuronium							
(1/30, 1/10)	Short	2.15**	D0	2.68**	D0	2.94**	D0
(1/90, 1/30)	Moderate	1.89**	D0	2.53**	D0	2.14**	D0
(1/270, 1/90)	Long	1.24**	1.1**	1.34**	0.82**	1.44**	0.31**
(1/810, 1/270)	Very Long	0.96**	1**	1.11**	0.9**	1.13**	0.87**
Labetalol							
(1/30, 1/10)	Short	0.88**	2.99**	0.88**	2.99**	0.88**	2.99**
(1/90, 1/30)	Moderate	0.93**	2.46**	0.93**	2.46**	0.93**	2.46**
(1/270, 1/90)	Long	0.93**	2.05**	0.94**	2.02**	0.94**	1.83**
(1/810, 1/270)	Very Long	0.98**	1.84**	0.98**	1.82**	0.98**	1.89**
Avastin							
(1/30, 1/10)	Short	1.12**	D0	1.12**	D0	1.12**	D0
(1/90, 1/30)	Moderate	1.08**	D0	1.08**	D0	1.08**	D0
(1/270, 1/90)	Long	0.86**	2.35**	0.88**	2.09**	0.95**	1.03**
(1/810, 1/270)	Very Long	0.95**	1.36**	0.95**	1.3**	0.97**	0.84**
Oxytocin							
(1/30, 1/10)	Short	3.04**	D0	3.04**	D0	4.05**	D0
(1/90, 1/30)	Moderate	1.9**	D0	1.9**	D0	2.4**	D0
(1/270, 1/90)	Long	1.3**	0.36**	1.31**	1.18**	1.43**	0.23**
(1/810, 1/270)	Very Long	0.98**	0.99**	0.98**	0.99**	1.11**	0.45**
Cefazolin							
(1/30, 1/10)	Short	8.42**	D0	8.36**	D0	9.56**	D0
(1/90, 1/30)	Moderate	4.53**	D0	5.05**	D0	6.21**	D0
(1/270, 1/90)	Long	1.44**	D0.01	1.59**	D0	1.66**	D0.07
(1/810, 1/270)	Very Long	1.02**	D0	1.12**	D0	1.2**	D0.02
Norepinephrine							
(1/30, 1/10)	Short	2.06**	D0	2.5**	D0	2.7**	D0
(1/90, 1/30)	Moderate	1.25**	D0.02	1.7**	D0	1.39**	D0.01
(1/270, 1/90)	Long	0.97**	0.04**	1.02**	0.06**	0.99*	0.03**
(1/810, 1/270)	Very Long	0.99**	1**	0.99**	1**	1	0.12**

Values represent the ratio of the proportion with the (D) Static model to the proportion with the (A) Adaptive model. Significance levels of 0.05 (*) and 0.01 (**) are indicated. When the proportion with the (A) Adaptive model or (D) Static model is zero, the value represents the difference between the two proportions (i.e., (A) Adaptive - (D) Static) and this is indicated with a "D" before the numerical value

$\frac{\alpha^{(1)}}{\alpha^{(1)}+\beta^{(1)}} = 0.25$). Fixing the long-run probability that the supply chain is disrupted, from top to bottom, the four supply chain disruption profiles are listed in order of increasing supply chain disruption duration.

In Table 5, we find that (e), for a fixed shortage-waste weighting and long-run probability that the supply chain is disrupted, if adaptive inventory policies are beneficial from a shortage [waste] perspective, the benefits generally decrease as the supply chain disruption duration increases. Similarly, if adaptive inventory policies are detrimental from a shortage [waste] perspective, the detriments generally decrease as the supply chain disruption duration increases. As an example, consider Labetalol with $(\delta_s, \delta_w) = (0.05, 0.05)$. The shortage ratio is less than 1 implying there are detriments in implementing the (A) Adaptive model in comparison to the (D) Static model. As the supply chain disruption duration increases (move down the rows of the table), we notice that the shortage ratio increases implying the detriments decrease. It is likely that the (D) Static model performs better than the (A) Adaptive model for Labetalol from a shortage perspective because this medication resembles a decreasing demand disruption (see Fig. 4(b)). Therefore, if we never change the inventory policy as done in the (D) Static model, we will always be over-ordering. Consequently, the (D) Static model leads to less shortages in comparison to the (A) Adaptive model that updates the inventory policy when changes in the mean demand occur. Keeping in mind that we are over-ordering with the (D) Static model, as we would expect, the (A) Adaptive model leads to a smaller proportion of drugs wasted per day in comparison to the (D) Static model which is seen with the waste ratio being greater than 1. We notice that as the supply chain disruption duration increases (move down the rows of the table), the waste ratio decreases implying the benefits decrease.

It is also worth noting that when a medication's inventory policy shifts from beneficial to detrimental as the supply chain disruption duration increases (e.g., see Avastin $(\delta_s, \delta_w) = (0.05, 0.05)$), the same conclusion (e) holds. Specifically, for these instances, as the supply chain disruption duration increases, the benefits of adaptive inventory policies decrease until the adaptive inventory policies become detrimental. When the adaptive inventory policies become detrimental, the detriments decrease as the supply chain disruption duration increases. Furthermore, when stating finding (e), we use the term generally because there are instances where the relationship does not hold exactly, but the difference in performance is very small (e.g., see Labetalol with $(\delta_s, \delta_w) = (0.025, 0.075)$ where $1.89 > 1.83$). Although, this is most likely a result of simulation sampling error.

We find that (f) as the expected supply chain disruption duration increases, the trade-off between drug shortages and drug waste becomes more apparent as improving one often negatively impacts the other. To see this finding, consider $(\delta_s, \delta_w) = (0.05, 0.05)$ for Rocuronium. We notice that the (A) Adaptive model is always beneficial from a shortage perspective as the shortage ratio is greater than 1. However, as the supply chain disruption duration increases, we notice that the (A) Adaptive model becomes detrimental from a waste perspective as the ratio is less than 1 illustrating the trade-off between drug shortages and drug waste.

The results from Table 5 also support the finding earlier that (a) for a fixed supply chain disruption profile, a medication's shortage-waste weighting dictates the magnitude of the benefits (or detriments) of adaptive inventory policies.

5.5 Ranking analysis

In Section 3.3, we present a P_{metric} ranking procedure that prioritizes medications and indicates which medications are of most concern. We proceed to describe a way of implementing the ranking procedure in practice and we analyze the performance when applying this method to the 500 highest (unit price)·(demand) medications at the University of Michigan's Central Pharmacy. We consider the total yearly demand when selecting the 500 highest (unit price)·(demand) medications. When considering the highest (unit price)·(demand) medications, we only consider medications that have demand data available for the time period of interest (i.e., October 2019-November 2021) and using this real-world demand data helps to capture the varying demand patterns that arise across medications. We ensure that the data only includes medications (e.g., removed medical supplies). 370 medications meet this criteria.

For implementation, we consider that the Central Pharmacy at the University of Michigan keeps record of P_{metric} every day for all medications. We consider that every 30 days, the Central Pharmacy decides which medications to update using the average value of P_{metric} over the most recent 30 days. However, instead of updating all medications that have an average value of P_{metric} greater than 0 (i.e., a value that signals a change in the (R, S) inventory policy is needed), we only allow the Central Pharmacy to update at most $M^{(\%)}$ percent of medications: $M^{(\%)} \in \{0, 2.5, 5, ..., 15\}$. If more than $M^{(\%)}$ percent of medications need to updated, we sort the average value of P_{metric} from largest to smallest for all medications, and we only update the top $M^{(\%)}$ percent of medications. For the analysis, we consider the input parameters defined in Section 5.3. But, we assume that all 503B medications have an expiration lifetime of 90 days which is consistent with the class of 503B medications (i.e., about 3 months) and we assume that all non-503B medications have an expiration lifetime of 360 days (i.e., about 1 year). Through discussions with our hospital pharmacy collabo-

rators, non-503B medications have a variety of expiration lifetimes and much longer lifetimes than 503B medications. We select 360 days for these medications because it is a conservative expiration lifetime estimate. Also, we consider $(\delta_s, \delta_w) = (0.05, 0.05)$ for the shortage-waste weighting, $(\alpha^{(1)}, \beta^{(1)}) = (\frac{1}{90}, \frac{1}{30})$ for the supply chain disruption profile, and we focus on the (A) Adaptive model where updates can only occur every 30 days (i.e., no buyback is in place). We present the average proportion of drug shortages per day across all medications and the average proportion of drugs wasted per day across all medications. We also present the cost of wasting a drug relative to the cost of a drug shortage that is required for the reduction in drug shortages to equally outweigh the detriments of drug waste. To calculate this value, we take the absolute difference between the average number of drug shortages with $M^{(\%)}$ percent and 0 percent updates across all medications divided by the absolute difference between the average number of drugs wasted with $M^{(\%)}$ percent and 0 percent updates across all medications. When the cost of wasting a drug relative to the cost of a drug shortage exceeds this value, it implies that the reduction in drug shortages does not outweigh the detriments of drug waste. Figure 8 illustrates the results.

We find that (g) there is a decreasing marginal benefit from a drug shortage perspective as the maximum percent of medications that can be updated increases. This implies that a decision-maker needs to update a very small proportion of medications at any point in time to get the greatest benefits of adaptive inventory policies. From a drug waste perspective, there is a decreasing marginal detriment as the maximum percent of medications that can be updated increases. However, the detriments from a drug waste perspective are very small practically speaking. Furthermore, with the results illustrating the trade-off between drug shortages and drug waste (i.e., decrease in drug shortages but increase in drug waste), we take a deeper look at the cost of wasting a drug relative to the cost of a drug shortage that is required for the reduction in drug shortages to equally outweigh the detriments of drug waste (see Fig. 8 row 3). We find that (h) the cost of wasting a drug would need to be far greater than the cost of a drug shortage for the reduction in drug shortages to not outweigh the detriments of drug waste. For example, consider $M^{\%} = 2.5$. The cost of wasting a drug would need to be about 3.5 times the cost of a drug shortage for the reduction in drug shortages to not outweigh the detriments of drug waste. Drug shortages can increase the cost of care, increase medication errors, and delay/cancel treatment [7]. Therefore, except for the few very high priced medications purchased on an order-by-order basis, it is highly unlikely that the cost of wasting a drug would be greater than a drug shortage let alone 3.5 times the cost of a drug shortage. It is worth noting that when we consider the 500 highest priced medications and the 500 highest demanded medications (total yearly demand), findings (g) and (h) continue to hold. Furthermore, if we consider the highest (unit price)·(demand) medications with all supply chain disruption profiles (i.e., $(\alpha^{(1)}, \beta^{(1)}) = \{(\frac{1}{30}, \frac{1}{10}), (\frac{1}{90}, \frac{1}{30}), (\frac{1}{270}, \frac{1}{90}), (\frac{1}{810}, \frac{1}{270})\}$) and shortage-waste weightings (i.e., $(\delta_s, \delta_w) \in \{(0.025, 0.075), (0.05, 0.05), (0.075, 0.025)\}$) combinations presented in Table 5, we continue to find similar trends to those stated in finding (g) for the proportion of drug shortages and proportion of drugs wasted except when $(\alpha^{(1)}, \beta^{(1)}) = (\frac{1}{810}, \frac{1}{270})$. When $(\alpha^{(1)}, \beta^{(1)}) = (\frac{1}{810}, \frac{1}{270})$, we find that the proportion of drug shortages and proportion

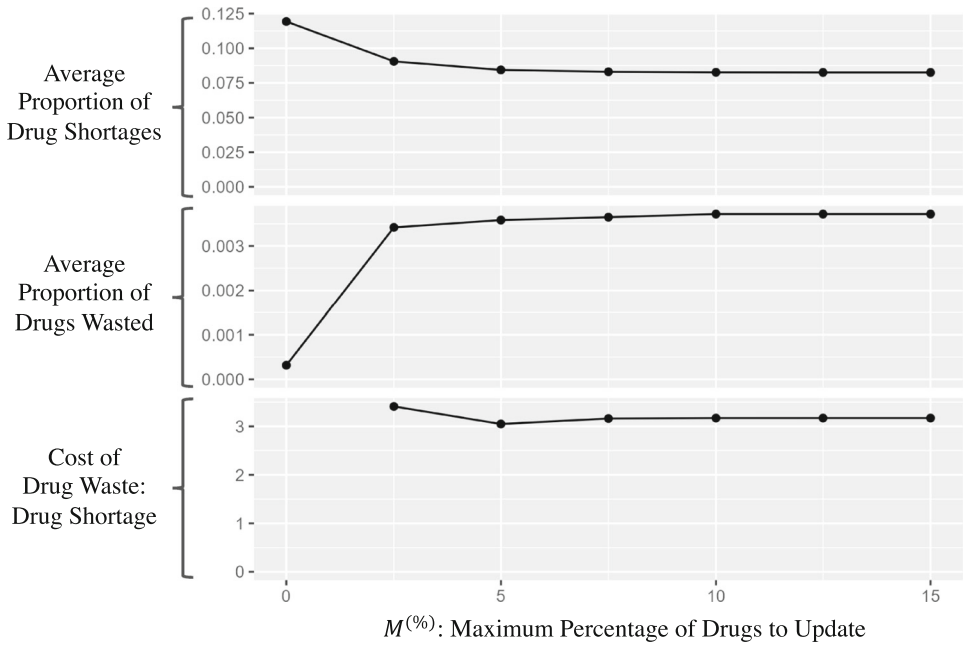


Fig. 8 Average proportion of drug shortages across all medications, average proportion of drugs wasted across all medications, and the cost of wasting a drug relative to the cost of a drug shortage that is required for the reduction in drug shortages to equally outweigh the detriments of drug waste. The analysis focuses on the highest (unit price)·(demand) medications at the University of Michigan's Central Pharmacy and for the analysis, a decision-maker can update at most $M^{(\%)}$ percent of medications every 30 days

of drugs wasted are fairly stable across the values of $M^{\%}$ that we consider. We note that this supply chain disruption profile implies that the expected duration of a supply chain disruption is 270 days (i.e., about $\frac{3}{4}$ of a year). In practice, when pharmacists begin to see these very long durations of supply chain disruptions, pharmacists will try to take corrective actions (e.g., shift to alternative treatment that is equally effective, shift to alternative dosage form such as an IV over oral, ration treatment) to minimize disturbances to the system.

5.6 Additional takeaways

We gain additional takeaways by analyzing (T1) the sensitivity of N (i.e., number of past daily demand observations used to estimate the expected daily demand) and (T2) the length of demand disruptions. Additional details are provided in Czerniak [44]. We find that:

(T1) It is important to have a large enough N to avoid high shortage and/or waste detriments, but not too large such that the benefits of an adaptive model start to decrease. Furthermore, a medication with a higher variability in demand (i.e., a larger standard deviation) often requires a larger N to avoid high shortage and/or waste detriments. As a rule of thumb, we suggest using about 50 daily demand observations when selecting N (e.g., $N = 49$, 7 weeks; $N = 56$, 8 weeks).

(T2) Given we vary the length of the demand disruption (for both increasing and decreasing demand disruptions), the benchmark model that only updates the inventory policy every $B = 90$ days using the average demand from the recent $B = 90$ days can lead to very poor performance. Furthermore, the adaptive model with buyback often performs better than the adaptive model without buyback for varying demand disruption lengths encouraging the use of such programs.

6 Conclusion

This research considers a perishable inventory system with supply chain disruptions and demand disruptions. This research leverages simulation modeling to distinguish how a medication's shortage-waste weighting (i.e., concern for shortages versus concern for waste) along with the duration of and time between supply chain disruptions influences the benefits (or detriments) of adapting to demand disruptions.

Managerial Insights

We find that when fixing the mean duration of and mean time between supply chain disruptions, a medication's shortage-waste weighting dictates the magnitude of the benefits (or detriments) of adaptive inventory policies. We also find that for a fixed shortage-waste weighting and long-run probability that the supply chain is disrupted, if adaptive inventory policies are beneficial from a shortage [waste] perspective, the benefits generally decrease as the supply chain disruption duration increases. Similarly, if adaptive inventory policies are detrimental from a shortage [waste] perspective, the magnitude of the negative impact of the adaptive inventory policies decreases as the supply chain disruption duration increases. Furthermore, when fixing the long-run probability that the supply chain is disrupted, we find that long supply chain disruption durations are the most sensitive to the trade-off between drug shortages and drug waste as improving one often negatively impacts the other. The results also suggest that hospital pharmacies should avoid updating the inventory policy on long fixed intervals and negotiate for buyback programs when establishing contracts with their suppliers/wholesalers. For the latter, this is under the assumption that a buyback program adds no additional costs to the hospital pharmacy inventory system. When looking at a large collection of medications, we find that a decision-maker needs to update a very small proportion of medications (e.g., $< 5\%$) at any point in time to get the greatest benefits of adaptive inventory policies.

Future Research

Our research illustrates that it is often beneficial for hospital pharmacies to participate in buyback programs. We do not consider buyback programs from the supplier perspective and we assume that the hospital pharmacy receives full compensation for the returned drug. If we assume that the hospital pharmacy does not receive full compensation for the returned drug, then the supplier may greatly benefit from buyback programs because they can possibly sell this collected drug to other hospital pharmacies at full price. However, there is no guarantee that another hospital pharmacy will purchase this returned drug before it expires. Hence, it would be interesting to study if the supplier should only accept a certain number of drugs or drugs with a certain remaining shelf life from the hospital pharmacy to reduce costs and waste at the supplier. We leave these studies for future research. Another area for future research is incorporating the relationship between substitute medications and demand disruptions into the adaptive inventory system. Through discussions with our hospital pharmacy collaborators, the demand disruptions for the 503B medications analyzed in Section 5.4.2 are a result of changes in the patient population during the Covid-19 pandemic. However, additional analyses (see Appendix Section D) illustrate that changes in the patient population for the primary medication may influence the demand for the substitute medication. In addition, we consider (R, S) inventory policies which are commonly implemented in practice. Future research can study other inventory policies

(e.g., (s, S) inventory policies) and how adapting these policies impact the performance of the inventory system. Furthermore, when considering (R, S) inventory policies, we assume full and accurate knowledge of the inventory on-hand. Future research can consider the case where inventory records are inaccurate [13]. A final direction for future research is using the adaptive inventory system presented in this research and analyzing how dynamic supply chain disruption parameters (i.e., $\alpha^{(1)}$ and $\beta^{(1)}$) influence the results.

Closing Thoughts

Decision-making is difficult in hospital pharmacy inventory systems due to perishability, supply chain disruptions, and demand disruptions. A medication's shortage-waste weighting and supply chain disruption profile influence the benefits (or detriments) of adapting to demand disruptions, and hospital pharmacy managers should consider these characteristics when implementing such policies in practice.

Appendix

A The (R, S) model

The (R, S) model provides the optimal length of the review period R^* and order-up-to level S^* in closed-form for a lost-sales perishable inventory system with supply chain disruptions.

A.1 Summary of the (R, S) model

We summarize the procedure presented in Czerniak et al. [30] to solve for a lost-sales (R, S) perishable inventory policy in a system with supply chain disruptions (two-state supply process). The four requirements that must be satisfied by the input parameters are $\gamma \leq \frac{\alpha^{(R)}}{\alpha^{(R)}+\beta^{(R)}}$, $\gamma > 0$, $\alpha^{(R)} > 0$, and $0 < \beta^{(R)} < 1$ (see Table 2). Also, the closed-form expressions treat the length of the review period (R) and the order-up-to level (S) as continuous decision variables.

Step 1: Solve for the Optimal m^*, R^*, and S^* for a Non-Perishable Inventory System

Using Eqs. A.1-A.3, solve for the optimal m^*, R^*, and S^*, respectively.

$$m^* = \left\lfloor \frac{\ln(\frac{(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})\gamma}{\alpha^{(R)}})}{\ln(1-\beta^{(R)})} \right\rfloor \tag{A.1}$$

$$R^* = \max\left\{1, \sqrt{\frac{2\alpha^{(R)}\beta^{(R)}(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})(1-\beta^{(R)})^{m^*}k}{qh(A_1+A_2)}}\right\} \tag{A.2}$$

where:

$$\begin{aligned}
A_1 &= m^*(2\alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m^*})(-\alpha^{(R)}\beta^{(R)} \\
&\quad + \alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m^*} + \beta^{(R)} + \alpha^{(R)} - (\beta^{(R)})^2) \\
A_2 &= (-2(\alpha^{(R)})^2\gamma - 2(\beta^{(R)})^2\gamma + 4(\beta^{(R)})^3\gamma - 2(\beta^{(R)})^4\gamma \\
&\quad + (\alpha^{(R)})^2\gamma^2 + (\beta^{(R)})^2\gamma^2 - 2(\beta^{(R)})^3\gamma^2 \\
&\quad + (\beta^{(R)})^4\gamma^2 - 4\alpha^{(R)}(\beta^{(R)})^2\gamma^2 \\
&-2(\alpha^{(R)})^2\beta^{(R)}\gamma^2 - 2(\alpha^{(R)})^2(\beta^{(R)})^2\gamma + 2\alpha^{(R)}(\beta^{(R)})^3\gamma^2 \\
&-4\alpha^{(R)}\beta^{(R)}\gamma + (\alpha^{(R)})^2(\beta^{(R)})^2\gamma^2 + 2\alpha^{(R)}\beta^{(R)}\gamma^2 \\
&\quad + 8\alpha^{(R)}(\beta^{(R)})^2\gamma \\
&\quad + 4(\alpha^{(R)})^2\beta^{(R)}\gamma - 4\alpha^{(R)}(\beta^{(R)})^3\gamma + 2(\alpha^{(R)})^2(\beta^{(R)})^2\gamma(1 \\
&-\beta^{(R)})^{m^*} - 2\alpha^{(R)}(\beta^{(R)})^2\gamma(1 \\
&-\beta^{(R)})^{m^*} - 2(\alpha^{(R)})^2\beta^{(R)}\gamma(1-\beta^{(R)})^{m^*} \\
&\quad + 2\alpha^{(R)}(\beta^{(R)})^3\gamma(1-\beta^{(R)})^{m^*} + (\alpha^{(R)})^2(1-\beta^{(R)})^{2m^*} \\
&\quad + 2\alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m^*} - 3\alpha^{(R)}(\beta^{(R)})^2(1-\beta^{(R)})^{m^*} \\
&-(\alpha^{(R)})^2\beta^{(R)}(1-\beta^{(R)})^{m^*} + \alpha^{(R)}(\beta^{(R)})^3(1-\beta^{(R)})^{m^*} \\
&\quad + (\alpha^{(R)})^2\beta^{(R)}(1-\beta^{(R)})^{2m^*} + (\alpha^{(R)})^2(\beta^{(R)})^2(1-\beta^{(R)})^{m^*})
\end{aligned}$$

$$S^* = qR^*\left(\frac{-\gamma(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)}) + \alpha^{(R)}(1-\beta^{(R)})^{m^*} + \alpha^{(R)}\beta^{(R)}m^*(1-\beta^{(R)})^{m^*}}{\alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m^*}}\right) \tag{A.3}$$

$$m^* = \left\lfloor \frac{\ln(\frac{(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})\gamma}{\alpha^{(R)}})}{\ln(1-\beta^{(R)})} \right\rfloor \tag{A.4}$$

$$R^* = \max\left\{1, \frac{e}{\frac{-\gamma(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})+\alpha^{(R)}(1-\beta^{(R)})^{m^*}+\alpha^{(R)}\beta^{(R)}m^*(1-\beta^{(R)})^{m^*}}{\alpha^{(R)}\beta^{(R)}(1-\beta^{(R)})^{m^*}}}\right\} \tag{A.5}$$

$$S^* = eq \tag{A.6}$$

Step 2: Check if $S^* \leq eq$

If $S^* \leq eq$, then m^*, R^*, and S^* found using Eqs. A.1-A.3 represent the optimal (R, S) inventory policy for the perishable inventory system. If $S^* > eq$, proceed to Step 3.

Step 3: Enforce the Perishability Condition by Setting $S^* = eq$

Using Eqs. A.4-A.6, solve for m^*, R^*, and S^*, respectively.

When $S^* \leq eq$ (i.e., the non-perishable model suffices; Step 3 is not necessary), the maximum proportion of drug shortages per day constraint (i.e., γ) is always satisfied because S^* depends on R^*. Further, the constraint for the maximum proportion of drug shortages per day is tight (i.e., maximum proportion of drug shortages per day equals γ). When the perishability condition is enforced (i.e., Step 3 is necessary), there may be instances where the maximum proportion of drug shortages per day constraint cannot be satisfied because S^* is constrained to eq and no longer depends on R^*. When the maximum proportion of drug shortages per day constraint cannot be satisfied, the optimal inventory policy is always $(R^* = 1, S^* = eq)$ (i.e., the smallest R^* and the largest S^*) as this maximizes the expected inventory on-hand.

When solving for the (R, S) inventory policy, the solutions are expressed in closed-form, but they are solved iteratively to account for a two-state supply process. The disruption probability (i.e., $\alpha^{(R)}$) and recovery probability (i.e., $\beta^{(R)}$) presented in Eqs. A.1-A.6 must be defined with respect to the length of the review period (R). However, the length of the review period is not known until solved using the closed-form expressions (i.e., Eqs. A.1-A.3 or A.4-A.6). Therefore, we implement the iterative algorithm for a two-state supply process presented in Czerniak et al. [30] where $\alpha^{(i)}$ and $\beta^{(i)}$ denote the disruption and recovery probability, respectively, for a review period of length i days. The algorithm takes $\alpha^{(1)}$ and $\beta^{(1)}$ as input (i.e., α and β are defined with respect to 1 day) and finds the appropriate values $\alpha^{(R)}$ and $\beta^{(R)}$ using the i-step transition probability matrix. We denote $\mathbf{P}^{(i)}$ as the i-step transition probability matrix (see Eq. A.7; [42]).

$$\mathbf{P}^{(i)} = \begin{pmatrix} \cdot & \alpha^{(i)} \\ \beta^{(i)} & \cdot \end{pmatrix} = \begin{pmatrix} (1-\alpha^{(1)}) & \alpha^{(1)} \\ \beta^{(1)} & (1-\beta^{(1)}) \end{pmatrix}^{i} \tag{A.7}$$

The full iterative algorithm is presented in the earlier research [30].

B Proportion metrics

We present how to calculate the expected proportion of drug shortages per day (in Appendix B.1) and the expected proportion of drugs wasted per day (in Appendix B.2).

B.1 Expected proportion of drug shortages

In Section 3.2.1 of the main paper, we present the expected proportion of drug shortages per day in Eq. 4. The expected proportion of drug shortages per day depends on the length of the review period (R), the order-up-to level (S), the expected daily demand $(\bar{q})$, the disruption probability $(\alpha^{(R)})$, and the recovery probability $(\beta^{(R)})$. Proportion is measured relative to the expected daily demand $\bar{q}$.

When deriving the closed-form (R, S) inventory policy solutions, Czerniak et al. [30] assume that $m = \lfloor \frac{S}{\bar{q}R} \rfloor \geq 1$ (i.e., S covers at least 1 review period; see Table 2 in Section 3.1). Therefore, when $m \geq 1$, we directly use the two-state supply process results found in Czerniak et al. [30]. When $m < 1$, the order-up-to level S does not cover a full review period (i.e., $\bar{q}R > S$). The expected proportion of drug shortages consists of two components: (a) the long-run probability that the supply chain is not disrupted (i.e., $\frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}$) multiplied by the expected number of drug shortages in a review period of length R (i.e., $\bar{q}R - S$) divided by the demand in a review period of length R (i.e., $\bar{q}R$) and (b) the long-run probability that the supply chain is disrupted (i.e., $1 - \frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}$) multiplied by 1. For (b), m does not cover a full review period, so any time the supply chain is disrupted, the inventory system has zero inventory on-hand resulting in an expected proportion of drug shortages per day of 1. We do not account for stochastic demand as past research illustrates that stochastic demand that is normally distributed has a negligible impact on the expected proportion of drug shortages per day with the (R, S) model.

B.2 Expected proportion of drugs wasted

In Section 3.2.1 of the main paper, we present the expected proportion of drugs wasted per day in Eq. 5. We calculate the expected proportion of drugs wasted given a (R, S) inventory policy with expected daily demand $\bar{q}$ and standard deviation of daily demand σ (i.e., $P_{waste|(\bar{q},\sigma,R,S)}$). We consider the expiration lifetime (e), the length of the review period (R), the order-up-to level (S), the expected daily demand $(\bar{q})$, the standard deviation of daily demand (σ), the disruption probability $(\alpha^{(R)})$, and the recovery probability $(\beta^{(R)})$. Proportion is measured relative to the expected number of drugs ordered.

To derive (5), we first consider the case with deterministic daily demand $\bar{q}$ and no supply chain disruptions. When we follow a (R, S) inventory policy for a perishable drug with expiration lifetime e, the inventory system follows a cyclic pattern where each cycle lasts $\lceil \frac{e}{R} \rceil \cdot R$ days. We note that the (R, S) model assumes $e \geq 1$ and $R \geq 1$. On day e in the cycle, we discard $\max\{0, S - e\bar{q}\}$ drugs. As a specific example, consider $R = 3$ days and $e = 5$ days. In Table 6, we present the cyclic pattern of the inventory system where we

Table 6 Cyclic pattern of the (R, S) inventory system with perishability

S	Day	Start. Inv.	Waste	Short	End Inv.	Age=1	Age=2	Age=3	Age=4	Order size
$\bar{q}$	1	$\bar{q}$	0	0	0	0	0	0	0	0
	2	0	0	$\bar{q}$	0	0	0	0	0	0
	3	0	0	$\bar{q}$	0	0	0	0	0	$\bar{q}$
$2\bar{q}$	1	$2\bar{q}$	0	0	$\bar{q}$	$\bar{q}$	0	0	0	0
	2	$\bar{q}$	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	$2\bar{q}$
$3\bar{q}$	1	$3\bar{q}$	0	0	$2\bar{q}$	$2\bar{q}$	0	0	0	0
	2	$2\bar{q}$	0	0	$\bar{q}$	0	$\bar{q}$	0	0	0
	3	$\bar{q}$	0	0	0	0	0	0	0	$3\bar{q}$
$4\bar{q}$	1	$4\bar{q}$	0	0	$3\bar{q}$	$3\bar{q}$	0	0	0	0
	2	$3\bar{q}$	0	0	$2\bar{q}$	0	$2\bar{q}$	0	0	0
	3	$2\bar{q}$	0	0	$\bar{q}$	0	0	$\bar{q}$	0	$3\bar{q}$
	4	$4\bar{q}$	0	0	$3\bar{q}$	$3\bar{q}$	0	0	0	0
	5	$3\bar{q}$	0	0	$2\bar{q}$	0	$2\bar{q}$	0	0	0
	6	$2\bar{q}$	0	0	$\bar{q}$	0	0	$\bar{q}$	0	$3\bar{q}$
$S \geq 5\bar{q}$	1	S	0	0	S-$\bar{q}$	S-$\bar{q}$	0	0	0	0
	2	S-$\bar{q}$	0	0	S-$2\bar{q}$	0	S-$2\bar{q}$	0	0	0
	3	S-$2\bar{q}$	0	0	S-$3\bar{q}$	0	0	S-$3\bar{q}$	0	$3\bar{q}$
	4	S	0	0	S-$\bar{q}$	$3\bar{q}$	0	0	S-$4\bar{q}$	0
	5	S-$\bar{q}$	S-$5\bar{q}$	0	$3\bar{q}$	0	$3\bar{q}$	0	0	0
	6	$3\bar{q}$	0	0	$2\bar{q}$	0	0	$2\bar{q}$	0	S-$2\bar{q}$
	7	S	0	0	S-$\bar{q}$	S-$2\bar{q}$	0	0	$\bar{q}$	0
	8	S-$\bar{q}$	0	0	S-$2\bar{q}$	0	S-$2\bar{q}$	0	0	0
	9	S-$2\bar{q}$	0	0	S-$3\bar{q}$	0	0	S-$3\bar{q}$	0	$3\bar{q}$
	10	S	0	0	S-$\bar{q}$	$3\bar{q}$	0	0	S-$4\bar{q}$	0
	11	S-$\bar{q}$	S-$5\bar{q}$	0	$3\bar{q}$	0	$3\bar{q}$	0	0	0
	12	$3\bar{q}$	0	0	$2\bar{q}$	0	0	$2\bar{q}$	0	S-$2\bar{q}$

vary S in increments of $\bar{q}$. We use the same table convention as presented in [29]. For $S < e\bar{q}$, the inventory system has a cycle of R days which is a factor of $\lceil \frac{e}{R} \rceil \cdot R$ and for $S \geq e\bar{q}$, the inventory system has a cycle of $\lceil \frac{e}{R} \rceil \cdot R$ days, so we simply conclude each cycle lasts $\lceil \frac{e}{R} \rceil \cdot R$ days.

We now formally define a cycle as a period of time such that on day e in the cycle, $\max\{0, S - e\bar{q}\}$ drugs are wasted. There is zero waste on all other days in the cycle. With deterministic daily demand $\bar{q}$ and no supply chain disruptions, we have the results presented in Eqs. B.1-B.2.

$$\begin{aligned} &\mathbb{E}[\text{no. of drugs wasted per cycle}] \\ &= \max\{0, S - e\bar{q}\} \end{aligned} \tag{B.1}$$

$$\begin{aligned} &\mathbb{E}[\text{no. of drugs ordered in a cycle}] \\ &= \overbrace{\lceil \frac{e}{R} \rceil R\bar{q}}^{\text{no. used}} + \overbrace{\max\{0, S - e\bar{q}\}}^{\text{no. wasted}} \end{aligned} \tag{B.2}$$

We next consider that we have deterministic daily demand $\bar{q}$ and supply chain disruptions that follow a two-state supply process. Given we have a supply chain disruption, we need to consider which day in the cycle the supply chain disruption begins to accurately calculate the number of drugs ordered in the cycle. Recall that a cycle lasts $\lceil \frac{e}{R} \rceil \cdot R$ days when the supply chain is not disrupted. Each cycle has $\lceil \frac{e}{R} \rceil$ days that correspond to a review period day. Given we know that a supply chain disruption occurs in the cycle, out of the $\lceil \frac{e}{R} \rceil$ days in the cycle that correspond to a review period day, there is an equal probability that the supply chain disruption begins on any of these review period days. Hence, the probability that the supply chain disruption starts on any review period day in the cycle is $\frac{1}{\lceil \frac{e}{R} \rceil}$. Taking into account the day the supply chain disruption starts in a cycle, we have the results presented in Eqs. B.3-B.4. π_j is the probability that the supply chain is disrupted for exactly j consecutive review periods $(\pi_0 = \frac{\beta^{(R)}}{\alpha^{(R)}+\beta^{(R)}}; \pi_j = \frac{\alpha^{(R)}\beta^{(R)}}{(\alpha^{(R)}+\beta^{(R)})(1-\beta^{(R)})}(1-\beta^{(R)})^j,\ j \geq 1)$.

$$\mathbb{E}[\text{no. of drugs wasted per cycle}] = \max\{0, S - e\bar{q}\} \tag{B.3}$$

$$\mathbb{E}[\text{no. of drugs ordered in a cycle}] = \tag{B.4}$$

$$\begin{cases} S; \quad \lceil \frac{e}{R} \rceil = 1 \\ (\lceil \frac{e}{R} \rceil R\bar{q} + \max\{0, S - e\bar{q}\})\pi_0 + \sum_{j=\lceil \frac{e}{R} \rceil - 1}^{\infty} \pi_j (S + R\bar{q}(\frac{(\lceil \frac{e}{R} \rceil - 1)}{2})); \quad \lceil \frac{e}{R} \rceil = 2 \\ (\lceil \frac{e}{R} \rceil R\bar{q} + \max\{0, S - e\bar{q}\})(\pi_0 + \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} \pi_j - \frac{1}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j\pi_j) + \frac{S}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j\pi_j + \frac{R\bar{q}}{\lceil \frac{e}{R} \rceil} \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j^2\pi_j \\ + \sum_{j=\lceil \frac{e}{R} \rceil - 1}^{\infty} \pi_j (S + R\bar{q}(\frac{(\lceil \frac{e}{R} \rceil - 1)}{2})); \quad \lceil \frac{e}{R} \rceil \geq 3 \end{cases}$$

where $\pi_0 = \dfrac{\beta^{(R)}}{\alpha^{(R)} + \beta^{(R)}}$

$$\sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} \pi_j = \frac{\alpha^{(R)}\beta^{(R)}}{\alpha^{(R)} + \beta^{(R)}} \left(\frac{1 - (1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 2}}{\beta^{(R)}} \right)$$

$$\sum_{j=\lceil \frac{e}{R} \rceil - 1}^{\infty} \pi_j = 1 - \sum_{j=0}^{\lceil \frac{e}{R} \rceil - 2} \pi_j = 1 - \pi_0 - \sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} \pi_j$$

$$\sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j\pi_j = \frac{\alpha^{(R)}\beta^{(R)}}{(\alpha^{(R)} + \beta^{(R)})(1 - \beta^{(R)})} \left(\frac{1 - (\lceil \frac{e}{R} \rceil - 1)(1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 2} + (\lceil \frac{e}{R} \rceil - 2)(1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 1}}{(\beta^{(R)})^2} \right)$$

$$\sum_{j=1}^{\lceil \frac{e}{R} \rceil - 2} j^2\pi_j = \frac{\alpha^{(R)}\beta^{(R)}}{(\alpha^{(R)} + \beta^{(R)})(1 - \beta^{(R)})} \left(\frac{1}{\beta^{(R)}} \right) \Bigg(- (1 - \beta^{(R)}) \left(\frac{1 - (1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 2}}{\beta^{(R)}} \right) - (\lceil \frac{e}{R} \rceil - 2)^2 (1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 1}$$
$$+ 2 \left(\frac{(1 - \beta^{(R)}) - (\lceil \frac{e}{R} \rceil - 1)(1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil - 1} + (\lceil \frac{e}{R} \rceil - 2)(1 - \beta^{(R)})^{\lceil \frac{e}{R} \rceil}}{(\beta^{(R)})^2} \right) \Bigg)$$

$$\mathbb{E}[\max\{0, S - \sum_{i=1}^{e} Q_i\}] = E_w = \Pr(\sum_{i=1}^{e} Q_i < S) \cdot (S - \mathbb{E}[\sum_{i=1}^{e} Q_i | \sum_{i=1}^{e} Q_i < S]) + \Pr(\sum_{i=1}^{e} Q_i \geq S) \cdot 0 \tag{B.5}$$

$$\mathbb{E}[\max\{0, S - \sum_{i=1}^{e} Q_i\}] = E_w = S \cdot \Pr(Z < \frac{S - e\bar{q}}{\sqrt{e\sigma^2}}) - e\bar{q} - \frac{1}{2\pi} \left(- e^{-\frac{(S - e\bar{q})^2}{2e\sigma^2}} + e^{-\frac{(-e\bar{q})^2}{2e\sigma^2}} \right) \sqrt{e\sigma^2} \tag{B.6}$$

Next, we incorporate stochastic demand where we assume that the daily demand is normally distributed with mean $\bar{q}$ and standard deviation σ. For the deterministic demand case, we have a demand of exactly $e\bar{q}$ in a period of e days. Thus, we waste exactly $\max\{0, S - e\bar{q}\}$ drugs in each cycle. When we have stochastic demand, we may not have a demand of exactly $e\bar{q}$ in a period of e days. Letting Q_i denote a normal random variable with mean $\bar{q}$ and standard deviation σ for the demand on day i, we consider the expectation of $\max\{0, S - e\bar{q}\}$ presented in Eq. B.5 and simplified in Eq. B.6. In Eq. B.6, we assume that $\sum_{i=1}^{e} Q_i \geq 0$ as demand is always non-negative. It is worth noting that Eq. B.6 can easily be modified to accommodate other probability distributions (e.g., Poisson) by using the appropriate expectation and cumulative distribution function.

Using Eq. B.6 in Eqs. B.3-B.4 and the relation presented in Eq. B.7, we have the expected proportion of drugs wasted per

day presented in Eq. 5 of the main paper. Equation 5 accounts for a (R, S) inventory system with supply chain disruptions that follow a two-state supply process and stochastic demand that is independent and normally distributed.

$$E_{waste|(\bar{q},\sigma,R,S)} = \frac{\mathbb{E}[\text{no. of drugs wasted per cycle}]}{\mathbb{E}[\text{no. of drugs ordered in a cycle}]} \tag{B.7}$$

C Numerical analysis: additional data

We proceed to present the weekly demand data for the four other 503B drugs of interest presented in Section 5.4 of the numerical analysis: Avastin, Oxytocin, Cefazolin, Norepinephrine (in Section C.1).

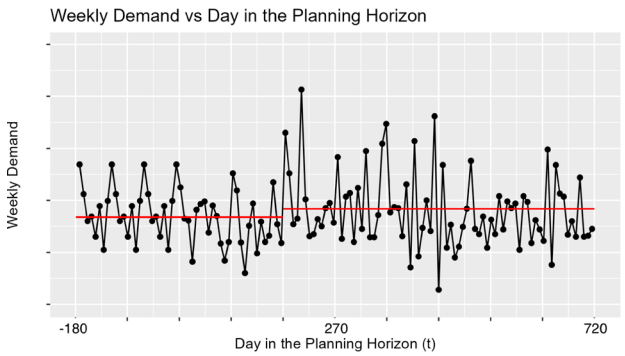
C.1 Weekly demand data for the other 503B drugs of interest

We present the weekly demand data for the four other 503B drugs of interest: Avastin 1.25mg/0.05mL (chemotherapy with several indications; see Fig. 9(a)), Oxytocin 30 units/500 mL (induction of labor; see Fig. 9(b)), Cefazolin 2gm/100mL (antibiotic; see Fig. 9(c)), Norepinephrine 16 mg/250mL (vasopressor used to increase blood pressure; see Fig. 9(d)). The red lines in the figures denote the corresponding mean weekly demand that minimizes the sum of squared errors for the daily demand data. For Avastin, Oxytocin, and Cefazolin, we consider two mean weekly demand values and for Norepinephrine, we consider three mean weekly demand values.

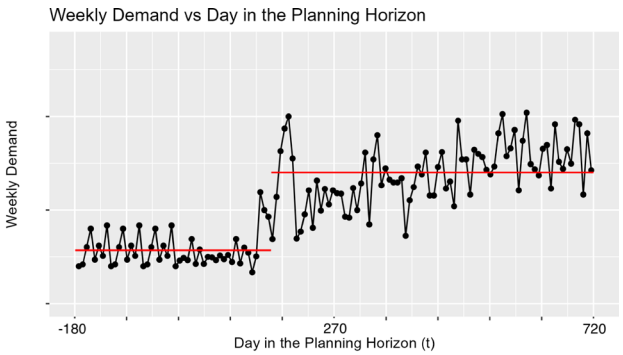
D Future research: substitute medications

An area for future research is incorporating the relationship between substitute medications and demand disruptions into the adaptive inventory system. We proceed to present an analysis for motivation.

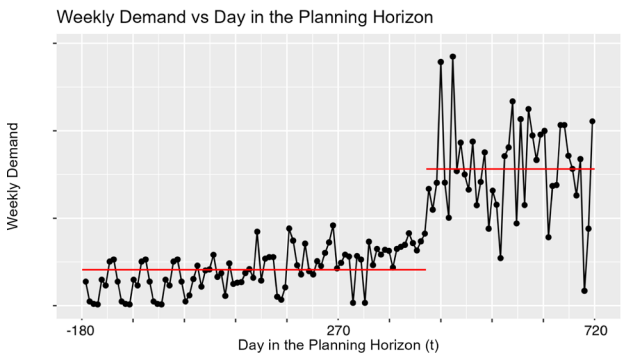
We first consider the 503B medication Rocuronium 10mg/1mL (i.e., Rocuronium (503B); see Section 5.1). If this 503B medication is not available, pharmacists will prescribe the non-503B medication Rocuronium 10mg/1mL vial (i.e., Substitute for Rocuronium (503B)). We second consider



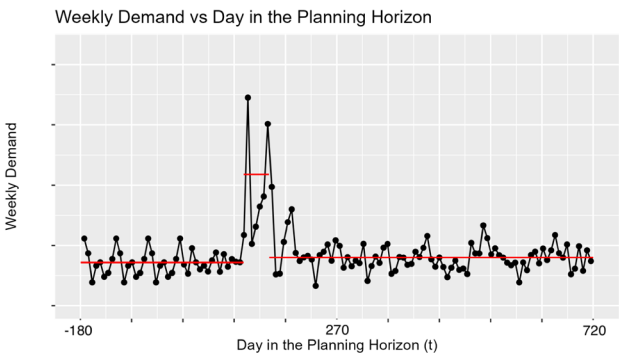
(a) Avastin.



(b) Oxytocin.

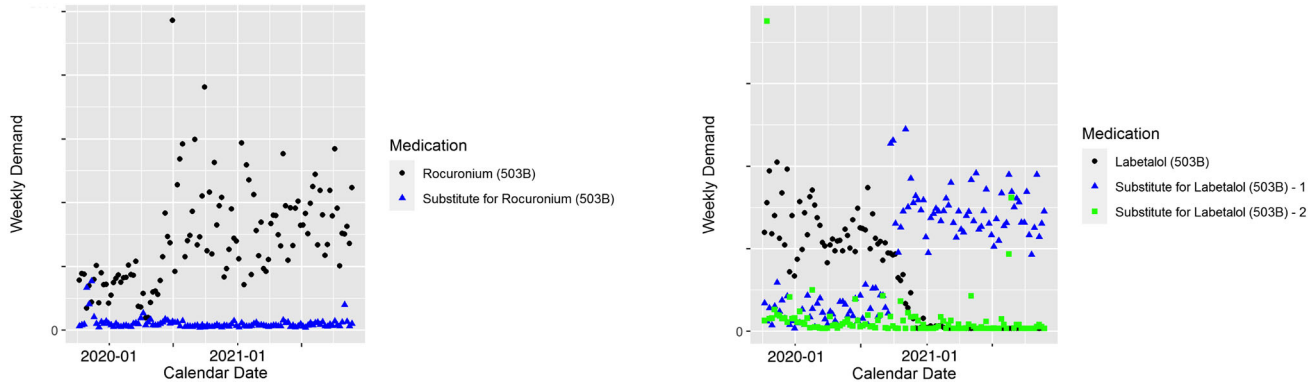


(c) Cefazolin.



(d) Norepinephrine.

Fig. 9 Weekly demand versus day in the planning horizon. We remove the weekly demand values on the y-axis for data confidentiality



(a) Rocuronium. (b) Labetalol.

Fig. 10 Weekly demand versus calendar date. Numerical values are removed on the y-axis for data confidentiality

the 503B medication Labetalol 5mg/1mL (i.e., Labetalol (503B); see Section 5.1). If this 503B medication is not available, pharmacists will prescribe Labetalol 5mg/mL injection carpuject syringe (i.e., Substitute for Labetalol (503B) - 1) or Labetalol 5mg/mL - 20 mL vial (i.e., Substitute for Labetalol (503B) - 2). Through discussions with our hospital pharmacy collaborators, beyond the substitutes described for each 503B medication, there are not great substitute medications because other medications in these classes have different clinical implications and concerns.

Using the real-world demand data provided by the University of Michigan's Central Pharmacy, we provide the weekly demand for Rocuronium (see Fig. 10(a)) and Labetalol (see Fig. 10(b)) from October 1, 2019 - November 22, 2021. We note that through discussions with our hospital pharmacy collaborators, the demand disruptions for Rocuronium (503B) and Labetalol (503B) are a result of changes in the patient population during the Covid-19 pandemic. When focusing on Labetalol (see Fig. 10(b)), we find that as the demand for Labetalol (503B) decreases, the demand for Substitute for Labetalol (503B) - 1 increases suggesting that changes in the patient population for the primary medication may influence the demand for the substitute medication.

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Availability of Data and Materials Due to confidentiality and privacy concerns, the demand data provided by the Central Pharmacy at the University of Michigan are not publicly available.

Declarations

Competing Interests The authors do not have non-financial conflicts of interest to disclose. For financial conflicts of interest, the first author was supported by the National Science Foundation Research Fellowship Program under Grant DGE 1841052.

Compliance with Ethical Standards This study has been exempt from the requirement for approval by an institutional review board because the research does not include human participants. The demand data used in this research does not include patient information.

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